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NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS	3	OCT 07	EPFULL enhanced with full implementation of EPC2000
NEWS	4	OCT 07	Multiple databases enhanced for more flexible patent number searching
NEWS	5	OCT 22	Current-awareness alert (SDI) setup and editing enhanced
NEWS	6	OCT 22	WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT Applications
NEWS	7	OCT 24	CHEMLIST enhanced with intermediate list of pre-registered REACH substances
NEWS	8	NOV 21	CAS patent coverage to include exemplified prophetic substances identified in English-, French-, German-, and Japanese-language basic patents from 2004-present
NEWS	9	NOV 26	MARPAT enhanced with FSORT command
NEWS	10	NOV 26	MEDLINE year-end processing temporarily halts availability of new fully-indexed citations
NEWS	11	NOV 26	CHEMSAFE now available on STN Easy
NEWS	12	NOV 26	Two new SET commands increase convenience of STN searching
NEWS	13	DEC 01	ChemPort single article sales feature unavailable
NEWS	14	DEC 12	GBFULL now offers single source for full-text coverage of complete UK patent families
NEWS	15	DEC 17	Fifty-one pharmaceutical ingredients added to PS
NEWS	16	JAN 06	The retention policy for unread STNmail messages will change in 2009 for STN-Columbus and STN-Tokyo
NEWS	17	JAN 07	WPIDS, WPINDEX, and WPIX enhanced Japanese Patent Classification Data

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NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

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DICTIONARY FILE UPDATES:   7 JAN 2009  HIGHEST RN 1092924-90-7

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=> E "ET-743"/CN 25
E1            2     ET-2/CN
E2            1     ET-2 (ALLOY)/CN
E3            0 --> ET-743/CN
E4            1     ET-BPOX/CN
E5            1     ET-CLEAN/CN
E6            1     ET-GLY-OBU-TERT/CN
E7            1     ET-J 1 SEALER TG/CN
E8            1     ET-K 5/CN
E9            1     ET-L 126/CN
E10           1     ET-SEMICON/CN
E11           1     ET3/CN
E12           1     ET35CO/CN
E13           1     ET4N(CPDS-TCNQ)2/CN
E14           1     ET9/CN
E15           4     ETA/CN
E16           1     ETA (ONIUM COMPOUND)/CN
E17           1     ETA (PESTICIDE)/CN
E18           1     ETA 100/CN
E19           1     ETA 12000/CN
E20           1     ETA 2/CN
E21           1     ETA 300/CN
E22           1     ETA 300-2-HYDROXYETHYL METHACRYLATE-NK ESTER APG
200-TRIMETHYLOLPROPANE TRIACRYLATE COPOLYMER/CN
E23           1     ETA 3041/CN
E24           1     ETA 3081/CN
E25           1     ETA 3163/CN

=> E "ET 743"/CN 25
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E1            1     ET 736 QUINONE/CN
E2            1     ET 736-CN/CN
E3            1 --> ET 743/CN
E4            1     ET 743 N12-OXIDE/CN
E5            1     ET 745/CN
E6            1     ET 75/CN
E7            1     ET 75 (PESTICIDE)/CN
E8            1     ET 75 (POLYMER)/CN
E9            1     ET 751/CN
E10           1     ET 757/CN
E11           1     ET 758/CN
E12           1     ET 759A/CN
E13           1     ET 759B/CN
E14           1     ET 76/CN
E15           1     ET 770/CN
E16           2     ET 8/CN
E17           1     ET 8 (POLYOLEFIN)/CN
E18           1     ET 8 (PROTECTIVE AGENT)/CN
E19           1     ET 8010/CN
E20           1     ET 81/CN
E21           1     ET 82/CN
E22           1     ET 83/CN
E23           1     ET 84/CN
E24           1     ET 840R/CN
E25           1     ET 85/CN

=> S E3
L1            1 "ET 743"/CN

=> DIS L1 1 SQIDE

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   114899-77-3  REGISTRY
CN   Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-
     dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one,
     5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-
     dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)-  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-
     dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one,
     5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-
     dimethoxy-4,10,23-trimethyl-, [6R-
     (6α,6aβ,7β,13β,14β,16α,20R*)]-
OTHER NAMES:
CN   Ecteinascidin 743
CN   Ecteinascidine 743
CN   Et 743
CN   NSC 648766
CN   Trabectedin
CN   Yondelis
FS   STEREOSEARCH
MF   C39 H43 N3 O11 S
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
       BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DRUGU,
       EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE,
       MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER,
       USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Conference; Dissertation; Journal; Patent
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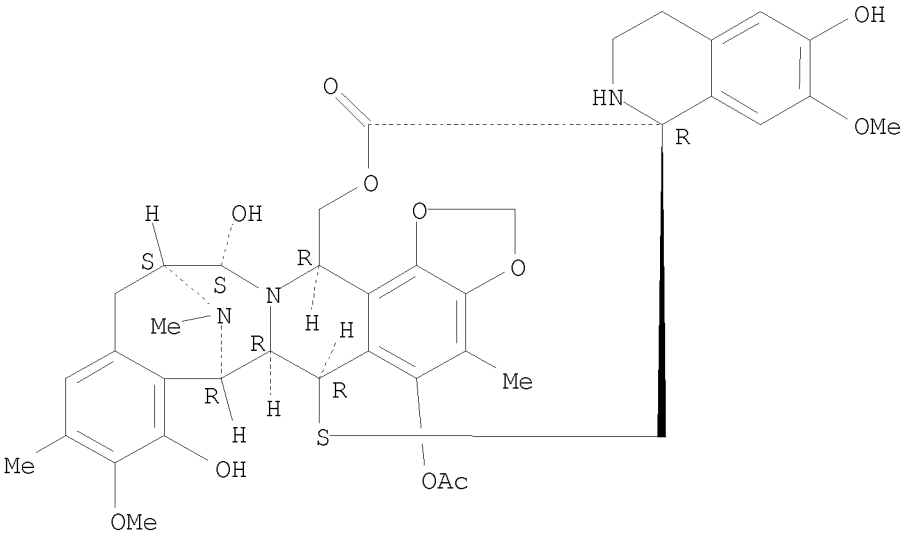
RL.P Roles from patents: BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry. Rotation (-).



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314 REFERENCES IN FILE CA (1907 TO DATE)
18 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
317 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline caplus wpids uspatfull

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FULL ESTIMATED COST	7.88	8.10

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FILE 'USPATFULL' ENTERED AT 14:02:33 ON 08 JAN 2009

=> s l1
L2 559 L1

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=> s l2 and (?cancer? or ?tumor? or ?tumour? or ?neoplasm? or ?carcin? or ?sarcom?)
L3         496 L2 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM? OR ?CARCIN
               ? OR ?SARCOM?)

=> s l3 and (intravenous or infusion)
L4         113 L3 AND (INTRAVENOUS OR INFUSION)

=> s l4 and ("3 weeks" or "4 weeks")
L5          38 L4 AND ("3 WEEKS" OR "4 WEEKS")

=> d l5 1-38 ibib, abs, hitstr

L5   ANSWER 1 OF 38     MEDLINE on STN
ACCESSION NUMBER:   2007733160     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 18000504
TITLE:              A Phase II study of trabectedin single agent in patients
                    with recurrent ovarian cancer previously treated
                    with platinum-based regimens.
AUTHOR:             Krasner C N; McMeekin D S; Chan S; Braly P S; Renshaw F G;
                    Kaye S; Provencher D M; Campos S; Gore M E
CORPORATE SOURCE:   Department of Medical Oncology, Massachusetts General
                    Hospital, Boston, MA, USA.. cnkrasner@partners.org
SOURCE:             British journal of cancer, (2007 Dec 17) Vol. 97, No. 12,
                    pp. 1618-24.  Electronic Publication: 2007-11-13.
                    Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      (CLINICAL TRIAL, PHASE II)
                    Journal; Article; (JOURNAL ARTICLE)
                    (RESEARCH SUPPORT, NON-U.S. GOV'T)
                    (CLINICAL TRIAL)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200802
ENTRY DATE:         Entered STN: 12 Dec 2007
                    Last Updated on STN: 15 Feb 2008
                    Entered Medline: 14 Feb 2008
AB   The objective of this study was to determine the objective response rate
     in patients with platinum-sensitive and platinum-resistant recurrent
     ovarian cancer to treatment with trabectedin (Yondelis)
     administered as a 3-h infusion weekly for 3
     weeks of a 4-week cycle.  We carried out a multicentre Phase II
     trial of trabectedin in patients with advanced recurrent ovarian
     cancer.  Trabectedin (0.58 mg m(-2)) was administered via a
     central line, after premedication with dexamethasone, to 147 patients as a
     3-h infusion weekly for 3 weeks followed by
     1-week rest.  Major eligibility criteria included measurable relapsed
     advanced ovarian cancer and not more than two prior
     platinum-containing regimens.  Patients were stratified according to the
     treatment-free interval (TFI) between having either platinum-sensitive
     (>/=6 months TFI) or platinum-resistant disease (<6 months
     TFI)/platinum-refractory disease (progression during first line therapy).
     In the platinum-sensitive cohort, 62 evaluable patients with measurable
     disease had an overall response rate (ORR) of 29.0% (95% CI: 18.2-41.9%)
     and median progression-free survival (PFS) was 5.1 months (95% CI:
     2.8-6.2).  Four patients with measurable disease per Response Evaluation
     Criteria in Solid Tumours (RECIST) criteria had no follow-up
     scans at the end of treatment.  In the platinum-resistant/refractory
     cohort, 79 patients were evaluable with an ORR of 6.3% (95% CI:
     2.1-14.2%).  Median PFS was 2.0 months (95% CI: 1.7-3.5 months).  Two
     patients with measurable disease per RECIST criteria had no follow-up
     scans at the end of treatment.  The most frequent (>/=2% of patients)
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drug-related treatment-emergent grade 3/4 adverse events were reversible liver alanine transferase elevation (10%), neutropaenia (8%), nausea, vomiting, and fatigue (5% each). Trabectedin is an active treatment, with documented responses in patients with platinum sensitive advanced relapsed ovarian cancer, and has a manageable toxicity profile.

L5 ANSWER 2 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2007636366 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17854236
TITLE: Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients.
AUTHOR: Perez-Ruixo Juan Jose; Zannikos Peter; Hirankarn Sarapee; Stuyckens Kim; Ludwig Elizabeth A; Soto-Matos Arturo; Lopez-Lazaro Luis; Owen Joel S
CORPORATE SOURCE: Clinical Pharmacology, Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium.. jjperez@umh.es
SOURCE: Clinical pharmacokinetics, (2007) Vol. 46, No. 10, pp. 867-84.
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(META-ANALYSIS)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200712
ENTRY DATE: Entered STN: 27 Oct 2007
Last Updated on STN: 28 Dec 2007
Entered Medline: 27 Dec 2007

AB OBJECTIVE: To characterise the population pharmacokinetics of trabectedin (ET-743, Yondelis(R)) in cancer patients. METHODS: A total of 603 patients (945 cycles) receiving intravenous trabectedin as monotherapy at doses ranging from 0.024 to 1.8 mg/m(2) and given as a 1-, 3- or 24-hour infusion every 21 days; a 1- or 3-hour infusion on days 1, 8 and 15 of a 28-day cycle; or a 1-hour infusion daily for 5 consecutive days every 21 days were included in the analysis. An open four-compartment pharmacokinetic model with linear elimination, linear and nonlinear distribution to the deep and shallow peripheral compartments, respectively, and a catenary compartment off the shallow compartment was developed to best describe the index dataset using NONMEM V software. The effect of selected patient covariates on trabectedin pharmacokinetics was investigated. Model evaluation was performed using goodness-of-fit plots and relative error measurements for the test dataset. Simulations were undertaken to evaluate covariate effects on trabectedin pharmacokinetics. RESULTS: The mean (SD) trabectedin elimination half-life was approximately 180 (61.4) hours. Plasma accumulation was limited when trabectedin was given every 3 weeks. Systemic clearance (31.5 L/h, coefficient of variation 51%) was 19.2% higher in patients receiving concomitant dexamethasone. The typical values of the volume of distribution at steady state for male and female patients were 6070L and 5240L, respectively. Within the range studied, age, body size variables, AST, ALT, alkaline phosphatase, lactate dehydrogenase, total bilirubin, creatinine clearance, albumin, total protein, Eastern Cooperative Oncology Group performance status and presence of liver metastases were not statistically related to trabectedin pharmacokinetic parameters. The pharmacokinetic parameters of trabectedin were consistent across the infusion durations and dose regimens evaluated. CONCLUSIONS: The integration of trabectedin pharmacokinetic data demonstrated linear elimination, dose-proportionality up to 1.8 mg/m(2) and time-independent pharmacokinetics. The pharmacokinetic impact of dexamethasone and sex covariates is probably

limited given the moderate to large interindividual pharmacokinetic variability of trabectedin. The antiemetic and hepatoprotective effects are still a valid rationale to recommend dexamethasone as a supportive treatment for trabectedin.

L5 ANSWER 3 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2007604979 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17927287
TITLE: Trabectedin : a review of its use in the management of soft tissue sarcoma and ovarian cancer.
AUTHOR: Carter Natalie J; Keam Susan J
CORPORATE SOURCE: Wolters Kluwer Health | Adis, Auckland, New Zealand.. demail@adis.co.nz
SOURCE: Drugs, (2007) Vol. 67, No. 15, pp. 2257-76. Ref: 80
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200801
ENTRY DATE: Entered STN: 12 Oct 2007
Last Updated on STN: 17 Jan 2008
Entered Medline: 16 Jan 2008
AB Trabectedin (Yondelis); ET-743) is an antineoplastic agent that was originally derived from the Caribbean marine tunicate Ecteinascidia turbinata and is now produced synthetically. It binds to the minor groove of DNA, disrupting the cell cycle and inhibiting cell proliferation. Intravenous trabectedin administered once every 3 weeks is approved as monotherapy in Europe for use in patients with advanced soft tissue sarcoma (STS) after failure of standard therapy with anthracyclines or ifosfamide, or who are unsuited to receive these agents. It also has orphan drug status in STS in the US and in ovarian cancer in the US and Europe, and is under investigation as combination therapy in patients with recurrent ovarian cancer.In clinical trials, trabectedin showed efficacy in the treatment of patients with advanced or metastatic STS, especially those with leiomyosarcoma or liposarcoma, as well as in women with platinum-sensitive advanced or recurrent ovarian cancer . In addition, its tolerability profile was generally manageable. The introduction of trabectedin expands the currently limited range of effective treatment options for patients with advanced or metastatic STS; trabectedin also has the potential to be a beneficial treatment for advanced or recurrent ovarian cancer.

L5 ANSWER 4 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2007340795 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17553201
TITLE: Phase II study of trabectedin in pretreated patients with advanced colorectal cancer.
AUTHOR: Paz-Ares Luis; Rivera-Herreros Fernando; Diaz-Rubio Eduardo; Garcia Margarita; Casado Esther; Cubedo Ricardo; Gravalos Cristina; Alfaro Vicente; Gomez Javier; Izquierdo Miguel Angel; Tabernero Josep
CORPORATE SOURCE: Medical Oncology Deparment, Hospital Universitario 12 de Octubre, Madrid, Spain.
SOURCE: Clinical colorectal cancer, (2007 May) Vol. 6, No. 7, pp. 522-8.
Journal code: 101120693. ISSN: 1533-0028.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)
(CLINICAL TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200707
ENTRY DATE: Entered STN: 8 Jun 2007
Last Updated on STN: 1 Aug 2007
Entered Medline: 31 Jul 2007

AB PURPOSE: This open-label, nonrandomized, phase II study was aimed at evaluating the efficacy and toxicity of trabectedin over a 3-hour intravenous infusion every 3 weeks in patients with pretreated advanced colorectal cancer. PATIENTS AND METHODS: Twenty-one patients were enrolled: 5 patients (23.8%) were treated with 1650 microg/m(2), 10 patients (47.6%) with 1300 microg/m(2), and 6 patients (28.6%) with 1100 microg/m(2). Response to treatment was assessed according to World Health Organization criteria, and toxicities were graded according to National Cancer Institute Common Toxicity Criteria, version 2.0. RESULTS: The median number of treatment cycles per patient was 2 (range, 1-6 cycles). No objective responses were reported. Four patients (19%; 95% confidence interval [CI], 5.5%-41.9%) exhibited stable disease lasting for a median of 3.6 months (range, 2.4-4.9 months). The median time to progression was 1.5 months (95% CI, 1.3-1.6 months), and the median overall survival was 4.4 months (95% CI, 3-7.5 months; n=2 censored). The main grade 3/4 toxicities were transient asymptomatic transaminase increase (alanine aminotransferase, 66.7% of patients; aspartate aminotransferase, 57.1%) and neutropenia (42.8%). No toxic deaths were reported. CONCLUSION: Trabectedin 1300 microg/m(2) given as a 3-hour intravenous infusion every 3 weeks was well tolerated but lacked activity in pretreated advanced-stage colorectal cancer. Therefore, further clinical trials with this trabectedin schedule as a single agent are not warranted.

L5 ANSWER 5 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2006546867 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16721129
TITLE: ET-743: a novel agent with activity in soft-tissue sarcomas.
AUTHOR: Fayette Jerome; Coquard Isabelle Ray; Alberti Laurent; Boyle Helen; Meeus Pierre; Decouvelaere Anne-Valerie; Thiesse Philippe; Sunyach Marie-Pierre; Ranchere Dominique; Blay Jean-Yves
CORPORATE SOURCE: Hopital Edouard Herriot, Service d'oncologie medicale, France.
SOURCE: Current opinion in oncology, (2006 Jul) Vol. 18, No. 4, pp. 347-53. Ref: 62
Journal code: 9007265. ISSN: 1040-8746.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200701
ENTRY DATE: Entered STN: 16 Sep 2006
Last Updated on STN: 17 Jan 2007
Entered Medline: 16 Jan 2007

AB PURPOSE OF REVIEW: ET-743 (ecteinascidin-743, trabectedin, Yondelis) is a natural marine product that has shown clinical activity in sarcoma . This paper reviews the current knowledge on this compound. RECENT FINDINGS: ET-743 interferes with several transcription factors, traps protein from the nucleotide-excision repair system, thus resulting in DNA damage, modulates gene expression, and blocks cells in the G2-M phase. In

the clinical setting, after failure of standard treatment, ET-743 at 1.5 mg/m2 in 24 h continuous infusion every 21 days yielded an overall response rate close to 8% and stabilization rates of 30-40%, some lasting beyond 3 years. Leiomyosarcomas, liposarcomas , and synovial sarcomas may be the more sensitive histotypes. The major toxicities of ET-743 are hepatic--through biliary duct destruction--and hematologic. They are not cumulative and a significant number of patients may receive 12 courses or more. In a randomized Phase II study testing weekly ET-743 with treatment every 3 weeks, an improved progression-free survival rate was observed in the 3-weekly arm; the results of the follow-up Phase III trial should be available at the American Society of Clinical Oncology meeting of 2006. Phase I combination studies are in currently progress. SUMMARY: ET-743 is a novel active drug for sarcoma which yields prolonged disease-free survival in subsets of patients.

L5 ANSWER 6 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2006499049 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16922593
TITLE: Trabectedin: Ecteinascidin 743, Ecteinascidin-743, ET 743, ET-743, NSC 684766.
AUTHOR: Anonymous
SOURCE: Drugs in R&D, (2006) Vol. 7, No. 5, pp. 317-28. Ref: 56
Journal code: 100883647. ISSN: 1174-5886.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 23 Aug 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 30 Nov 2006

AB Trabectedin [Ecteinascidin 743, Yondelis, ET 743, NSC 684766] is a tetrahydroisoquinoline alkaloid derived from the Caribbean marine tunicate, Ecteinascidia turbinata. The drug is being developed by PharmaMar (Zeltia) in partnership with Johnson & Johnson Pharmaceutical Research & Development LLC. It was synthetically isolated and developed by the University of Illinois and licensed to PharmaMar; the company has completed the hemisynthesis of agent. Trabectedin interacts with the minor groove of DNA and alkylates guanine at the N2 position, which bends towards the major groove. In this manner, it is thought that the drug affects various transcription factors involved in cell proliferation, particularly via the transcription-coupled nucleotide excision repair system. Trabectedin blocks the cell cycle at the G(2) phase, while cells at the G(1)phase are most sensitive to the drug. It also inhibits overexpression of the multidrug resistance-1 gene (MDR-1) coding for the P-glycoprotein that is a major factor responsible for cells developing resistance to cancer drugs. The agent is also thought to interfere with the nucleotide excision repair pathways of cancer cells, suggesting that it could be effective in the treatment of many cancer types including melanoma and sarcoma, as well as lung, breast, ovarian, endometrial and prostate cancers; clinical evaluations are underway in these indications. PharmaMar and Ortho Biotech Products (Johnson & Johnson) entered into an agreement in August 2001 for the joint development and commercialisation of trabectedin. PharmaMar retains commercialisation rights in Europe, including Eastern Europe. Ortho Biotech will market the product in the US, Japan and the rest of the world; Tibotec Therapeutics (a division of Ortho Biotech) will commercialise it in the US. PharmaMar will receive an initial payment from Ortho Biotech plus future milestone and royalty payments linked to development targets and sales; the upfront payment

would be approximately 20 million US dollars with royalties contributing 10-20% of total sales of the drug. Although details of the licensing transaction for trabectedin were undisclosed, analysts estimate the figure to be around 100 million US dollars. Previously, PharmaMar signed an agreement granting Bristol-Myers Squibb the option to evaluate and develop as many as 12 of PharmaMar's marine-derived anticancer compounds on an exclusive worldwide basis. However, it appears that Bristol-Myers Squibb had chosen not to exercise the option. Trabectedin is undergoing clinical trials in soft tissue sarcoma (Sarcoma in the Phase table), ovarian, breast, endometrial, prostate and non-small-cell lung cancers. PharmaMar indicated in January 2004 that it intends to launch trabectedin in one of these indications in 2006. PharmaMar raised funds from a round of financing in June 2005 that will be used to fund further clinical trials of its anticancer products, including trabectedin. The US FDA granted trabectedin orphan drug status for ovarian cancer in April 2005. Trabectedin also received orphan drug status from the European Commission for the treatment of ovarian cancer in October 2003. This followed a positive opinion by the Committee for Orphan Medicinal Products (COMP) of the EMEA. Trabectedin has undergone a phase II study for the second- or third-line treatment of ovarian cancer in Europe (England and Belgium), the US and Canada. The trial was initiated in October 2002 and evaluated a weekly schedule of trabectedin (0.58 mg/m(2)) via IV infusion for 3 weeks followed by a week of rest. Final results from this study have been presented. A separate phase II trial evaluating the antitumour activity of trabectedin as a second-line therapy in advanced ovarian cancer was conducted by researchers at the Southern Europe New Drugs Organization (SENDO) in Milan, Italy. PharmaMar and Johnson & Johnson are conducting a pivotal (STS-201) trial to compare a weekly and daily dosing regimen of trabectedin among patients with advanced or metastatic soft tissue sarcoma who are unresponsive to standard chemotherapy of doxorubicin and ifosfamide. The randomised, multicentre, open-label trial has completed enrolment of 270 patients during the second quarter of 2005. Positive data from the STS-201 trial have been announced. An independent data monitoring committee has found that interim data supports a positive trend in time to disease progression favouring patients receiving the daily dosing regimen. Consequently, all patients have been offered the option of switching to the daily regimen. Final results from the STS-201 trial will form the basis of MAA re-submission with European regulatory authorities. PharmaMar has held a pre-submission meeting with the EMEA and has presented a formal letter of intent to file for approval of trabectedin for soft tissue sarcoma . Previously, PharmaMar first filed for EU registration of trabectedin for treatment of advanced soft tissue sarcoma in November 2001, which was accepted for review by the EMEA and Swiss Health Authorities. However, the CPMP confirmed its recommendation not to grant trabectedin marketing authorisation in November 2003 following PharmaMar's appeal against the CPMP's negative opinion first announced in July 2003; the opinion was adopted by a majority vote rather than by consensus. Trabectedin was granted orphan drug status in Europe for recurrent soft tissue sarcoma in 2001. It was also granted orphan drug status by the FDA for the same indication in October 2004. Phase I studies are being conducted to evaluate trabectedin in combination with doxorubicin and liposomal doxorubicin for the treatment of soft tissue sarcoma . PharmaMar is also conducting a phase I study of sequential paclitaxel followed by trabectedin in patients with soft tissue sarcoma. At additional dose levels, patients with other tumour types will be enrolled to assess the antitumour activity of the combination. The US NCI has approved and is partially funding a phase I clinical programme to determine the feasibility of using trabectedin to treat children with soft tissue sarcoma and bone sarcoma who are resistant to conventional therapies. PharmaMar has reported that

trabectedin can be safely administered to children at doses up to 1100mg given as a 3-hour infusion, and that this dose will be used in further paediatric studies. Trabectedin has completed phase II studies for small round cell sarcoma and rhabdomyosarcoma, which are aggressive tumours occurring predominantly in children. A phase II study evaluating two dosing schedules of trabectedin has been conducted in patients with leiomyosarcomas or liposarcomas refractory to standard doxorubicin + ifosfamide chemotherapy. The study was conducted in Australia, Canada, Russia and the US.

L5 ANSWER 7 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2006307344 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16736024
TITLE: A phase II study of Yondelis (trabectedin, ET-743) as a 24-h continuous intravenous infusion in pretreated advanced breast cancer.
AUTHOR: Zelek L; Yovine A; Brain E; Turpin F; Taamma A; Riofrio M; Spielmann M; Jimeno J; Misset J L
CORPORATE SOURCE: Department of Medicine, Institut Gustave-Roussy, Villejuif, France.. laurent.zelek@hmn.aphp.fr
SOURCE: British journal of cancer, (2006 Jun 5) Vol. 94, No. 11, pp. 1610-4.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(CLINICAL TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 1 Jun 2006
Last Updated on STN: 17 Aug 2006
Entered Medline: 16 Aug 2006

AB Yondelis (trabectedin, ET-743) is a novel marine-derived anticancer compound found in the ascidian Ecteinascidia turbinata. It is currently under phase II/III development in breast cancer, hormone refractory prostate cancer, sarcomas and ovarian cancer. Activity in breast cancer experimental models has been reported, and preliminary evidence of activity in this setting during the phase I programme has also been observed. The present study assessed the activity and feasibility of trabectedin in women with advanced breast cancer previously treated with conventional therapies. Patients with advanced disease previously treated with at least one but not more than two regimens that included taxanes or anthracyclines as palliative therapy were eligible. Trabectedin 1.5 mg m(-2) was administered as a 24-h continuous infusion every 3 weeks. Patients were kept on therapy until disease progression, unacceptable toxicity or patient refusal. Twenty-seven patients were included between April 1999 and September 2000. Their median age was 54 years (range: 36-67) and 63% of them had two metastatic sites. Twenty-two patients were performance status 1. All patients had previously received anthracyclines, and 23 out of 27 patients had received taxanes. Of 21 patients with measurable disease, three confirmed partial responses, one unconfirmed partial response and two minor responses (49 and 32% tumour shrinkage) were observed; six patients had stable disease. Median survival was 10 months (95% confidence interval: 4.88-15.18). Transient and noncumulative transaminitis was observed in most of the patients. The pharmacokinetic profile of trabectedin in this patient's population is in line with the overall data available with this schedule. The policy of dose adjustments

based on the intercycle peaks of bilirubin and alkaline phosphatase appears to have a positive impact in the therapeutic index of trabectedin. Trabectedin can induce response and tumour control in previously treated advanced breast cancer, with manageable toxicity, thus warranting further development as a single agent or in combination regimens.

L5 ANSWER 8 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2005143214 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15774779
TITLE: Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails.
AUTHOR: Sessa Cristiana; De Braud Filippo; Perotti Antonella; Bauer Jean; Curigliano Giuseppe; Noberasco Cristina; Zanaboni Flavia; Gianni Luca; Marsoni Silvia; Jimeno Jose; D'Incalci Maurizio; Dall'o Elisa; Colombo Nicoletta
CORPORATE SOURCE: Southern Europe New Drugs Organization Foundation, Via Visconti di Modrone 12, 20100 Milano, Italy.. marsonis@sendo-org.it
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2005 Mar 20) Vol. 23, No. 9, pp. 1867-74.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 19 Mar 2005
Last Updated on STN: 6 Apr 2005
Entered Medline: 5 Apr 2005
AB PURPOSE: To assess the efficacy and toxicity of the marine-derived alkaloid trabectedin (ET-743) in patients with advanced ovarian cancer refractory to or experiencing disease relapse after platinum- and taxane-based chemotherapy. PATIENTS AND METHODS: Fifty-nine patients from four institutions either resistant (n = 30) or sensitive (n = 29) to prior platinum and taxanes were treated with a 3-hour infusion of trabectedin every 3 weeks.
Patients were monitored weekly for toxicity and restaged every two cycles for response. Response was assessed according to Response Evaluation Criteria in Solid Tumors Group. RESULTS: The peer-reviewed objective response rate in platinum-sensitive patients was 43% (95% CI, 23% to 65%) with an estimated median time to progression of 7.9 months (95% CI, 7.5 to 14.1 months); in platinum-resistant patients two partial responses were observed. Responses were durable for up to 12.9 months (median, 5 months). The predominant toxicities at the recommended dose of 1,300 microg/m(2) were neutropenia, asthenia, and self-limited increase of aminotransferases never requiring treatment interruption. CONCLUSION: Trabectedin administered as a 3-hour infusion at 1,300 microg/m(2) is a safe new drug with promising activity in relapsed ovarian cancer, showing a 43% objective response rate in patients with platinum-sensitive disease, which favorably compares with other salvage treatments and warrants additional development either alone or in combination.

L5 ANSWER 9 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2005033123 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15659504

TITLE: Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial.
AUTHOR: Le Cesne A; Blay J Y; Judson I; Van Oosterom A; Verweij J; Radford J; Lorigan P; Rodenhuis S; Ray-Coquard I; Bonvalot S; Collin F; Jimeno J; Di Paola E; Van Glabbeke M; Nielsen O S
CORPORATE SOURCE: Department of Medicine, Institut Gustave Roussy, 94805 Villejuif Cedex, France.. lecesne@igr.fr
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2005 Jan 20) Vol. 23, No. 3, pp. 576-84.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 25 Jan 2005
Last Updated on STN: 12 Mar 2005
Entered Medline: 11 Mar 2005

AB PURPOSE: This nonrandomized multicenter phase II study was performed to evaluate the activity and safety of Ecteinascidin (ET-743) administered at a dose of 1.5 mg/m(2) as a 24-hour continuous infusion every 3 weeks in patients with pretreated advanced soft tissue sarcoma. PATIENTS AND METHODS: Patients with documented progressive advanced soft tissue sarcoma received ET-743 as second- or third-line chemotherapy. Antitumor activity was evaluated every 6 weeks until progression, excessive toxicity, or patient refusal. RESULTS: One hundred four patients from eight European institutions were included in the study (March 1999 to November 2000). A total of 410 cycles were administered in 99 assessable patients. Toxicity mainly involved reversible grade 3 to 4 asymptomatic elevation of transaminases in 40% of patients, and grade 3 to 4 neutropenia was observed in 52% of patients. There were eight partial responses (PR; objective regression rate, 8%), 45 no change (NC; > 6 months in 26% of patients), and 39 progressive disease. A progression arrest rate (PR + NC) of 56% was observed in leiomyosarcoma and 61% in synovialosarcoma. The median duration of the time to progression was 105 days, and the 6-month progression-free survival was 29%. The median duration of survival was 9.2 months. CONCLUSION: ET-743 seems to be a promising active agent in advanced soft tissue sarcoma, with no cumulative toxicities. The 6-months progression-free survival observed in advanced soft tissue sarcoma compares favorably with those obtained with other active drugs tested in second-line chemotherapy in previous European Organisation for the Research and Treatment of Cancer trials. The median overall survival was unusually long in these heavily pretreated patients mainly due to the high number of patients who benefit from the drug in terms of tumor control.

L5 ANSWER 10 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2004278231 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15177491
TITLE: A phase II study of ET-743/trabectedin ('Yondelis') for patients with advanced gastrointestinal stromal tumours.
AUTHOR: Blay J-Y; Le Cesne A; Verweij J; Scurr M; Seynaeve C; Bonvalot S; Hogendoorn P; Jimeno J; Evrard V; van Glabbeke

M; Judson I
CORPORATE SOURCE: Hop Edouard Herriot and INSERM U590 Centre Leon Berard, Lyon, France.
SOURCE: European journal of cancer (Oxford, England : 1990), (2004 Jun) Vol. 40, No. 9, pp. 1327-31.
Journal code: 9005373. ISSN: 0959-8049.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 6 Jun 2004
Last Updated on STN: 25 Aug 2004
Entered Medline: 24 Aug 2004

AB Primary or secondary resistance to imatinib may occur in patients with gastrointestinal stromal tumours (GISTs) while these tumours have repeatedly been shown to be highly resistant to conventional doxorubicin- and ifosfamide-containing regimens. The investigation of new drugs is therefore warranted in GIST. A phase II study was conducted between May 1999 and November 2000 in eight centres of the EORTC STBSG group to establish the efficacy and safety of ET743 ('Yondelis') in GIST previously untreated with cytotoxic chemotherapy before the imatinib era. ET-743 was given was given at 1.5 mg/m(2) per course as a 24-h continuous intravenous infusion every 3 weeks. Twenty-eight patients were included, 16 males and 12 females. Median age was 54 years (range 25-73 years). Median performance status was 0 (range 0-1). 17 (63%), 4 (12%) and 7 (25%) patients, received 0-2, 3-5, and > or = 6 courses of ET-743, respectively. The best response was stable disease in 9 (33%) patients, and disease progression in 18 patients (67%), with a median time to disease progression and overall survival of 51 days and 589 days, respectively. The treatment was well tolerated: there were grades 3-4 neutropenia, thrombocytopenia, and transaminase increases in 13 (48%), 1 (4%) and 16 (59%) patients, respectively. There were no toxic deaths. ET-743 at this dose and schedule is not an effective treatment for advanced GIST.

L5 ANSWER 11 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2004188963 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15084621
TITLE: Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy.
AUTHOR: Garcia-Carbonero R; Supko J G; Manola J; Seiden M V; Harmon D; Ryan D P; Quigley M T; Merriam P; Canniff J; Goss G; Matulonis U; Maki R G; Lopez T; Puchalski T A; Sancho M A; Gomez J; Guzman C; Jimeno J; Demetri G D
CORPORATE SOURCE: Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Shields Warren Bldg, Room G530, 44 Binney St, Boston, MA 02115, USA.. gdemetri@partners.org
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2004 Apr 15) Vol. 22, No. 8, pp. 1480-90.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)

(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 16 Apr 2004
Last Updated on STN: 10 May 2004
Entered Medline: 7 May 2004

AB PURPOSE: To assess the efficacy of the marine-derived alkaloid ecteinascidin 743 (ET-743) in patients with soft tissue sarcomas that progressed despite prior conventional chemotherapy and to characterize the pharmacokinetic profiles of ET-743 in this patient population. PATIENTS AND METHODS: Thirty-six previously treated soft tissue sarcoma patients from three institutions received ET-743 as a 24-hour continuous intravenous (IV) infusion at a dose of 1,500 microg/m(2) every 3 weeks. Pharmacokinetic studies were also performed. Patients were restaged every two cycles for response by objective criteria. RESULTS: Objective responses were observed in three patients, with one complete response and two partial responses, for an overall response rate of 8% (95% CI, 2% to 23%). Responses were durable for up to 20 months. Two minor responses (43% and 47% tumor reduction) were observed, for an overall clinical benefit rate of 14%. The predominant toxicities were neutropenia and self-limited transaminitis of grade 3 to 4 severity in 34% and 26% of patients, respectively. The estimated 1-year time to progression and overall survival rates were 9% (95% CI, 3% to 27%) and 53% (95% CI, 39% to 73%), respectively. The maximum observed plasma concentration and total plasma clearance of ET-743 (mean +/- standard deviation), 1.04 +/- 0.48 ng/mL and 35.6 +/- 16.2 L/h/m(2), respectively, were consistent with previously reported values from phase I studies of the drug given as a 24-hour IV infusion. CONCLUSION: ET-743 is a promising new option for the management of several histologic subtypes of sarcoma. Durable objective responses were obtained in a subset of sarcoma patients with disease progression despite prior chemotherapy. Additionally, the relatively high survival rate noted in this series of previously treated patients further justifies development of this agent.

L5 ANSWER 12 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2004100806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14990645
TITLE: Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients.
AUTHOR: Yovine A; Riofrio M; Blay J Y; Brain E; Alexandre J; Kahatt C; Taamma A; Jimeno J; Martin C; Salhi Y; Cvitkovic E; Misset J L
CORPORATE SOURCE: Hopital St Louis, Unite d'Oncologie Medicale, 1 av. Claude Vellefaux, 75010 Paris, France..
jean-louis.misset@sls.ap-hop-paris.fr
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2004 Mar 1) Vol. 22, No. 5, pp. 890-9.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
(COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403

ENTRY DATE: Entered STN: 2 Mar 2004
Last Updated on STN: 25 Mar 2004
Entered Medline: 24 Mar 2004

AB PURPOSE: A multicenter phase II study evaluating efficacy, safety, and pharmacokinetics of ecteinascidin-743 (ET-743) in pretreated advanced soft tissue sarcoma patients. PATIENTS AND METHODS: Patients received ET-743 1,500 microg/m(2) (24-hour intravenous infusion) every 3 weeks (group 1, 26 patients with one to two prior single agents or one previous combination chemotherapy; group 2, 28 patients with three or more prior single agents or two or more previous combination chemotherapies). Results Patients (30 women, 24 men) had a median age of 48 years (range, 22 to 71 years); 41% had leiomyosarcoma (eight of 22 of uterine origin), a median of two involved organs (range, one to four), and 93% had documented progressive disease at study entry. Patients received a median of three cycles (range, one to 20); 28% received six or more cycles. Fifty-two patients were assessable for response (WHO criteria): two partial responses, four minor responses, and nine with stable disease (> or = 6 months). Three patients were rendered tumor free after surgery. Median progression-free survival was 1.9 months (range, 0.69 to 17.90 months); 24% of patients were progression free at 6 months. Median survival was 12.8 months, with 30% of patients alive at 2 years. Four patients withdrew because of treatment-related toxicity. Two treatment-related deaths occurred (renal failure and febrile neutropenia, and rhabdomyolysis and decompensated cirrhosis, respectively) that were probably related to protocol eligibility violations. Reversible grade 3 to 4 AST or ALT occurred in 50% of patients and grade 3 to 4 neutropenia occurred in 61% of patients, with six episodes of febrile neutropenia. Nausea, vomiting, and asthenia were prevalent but mild and manageable. CONCLUSION: With a 4% overall response rate (95% CI, 0.5 to 12.8) and an 11% rate of third-party-verified tumor regression (overall response rate + minor response), ET-743 has a 24% 6-month disease progression control rate, confirming evidence of antitumoral activity and a manageable safety profile in patients experiencing disease progression with pretreated soft tissue sarcoma.

L5 ANSWER 13 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003523145 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14599461
TITLE: Use of CFU-GM assay for prediction of human maximum tolerated dose of a new antitumoral drug: Yondelis (ET-743).
AUTHOR: Gomez Susana G; Bueren Juan A; Faircloth Glynn; Albella Beatriz
CORPORATE SOURCE: PharmaMar, S.A. Poligono Industrial La Mina, Avda de los Reyes, 1. 28770 Colmenar Viejo, Madrid, Spain.
SOURCE: Toxicology in vitro : an international journal published in association with BIBRA, (2003 Oct-Dec) Vol. 17, No. 5-6, pp. 671-4.
Journal code: 8712158. ISSN: 0887-2333.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 6 Nov 2003
Last Updated on STN: 7 Jul 2004
Entered Medline: 6 Jul 2004

AB Acute cytotoxic exposure causes decreases in bone marrow progenitors that precedes the neutrophil nadir. Experiments in animal models reveal a relationship between the reduction in granulocyte-macrophage progenitors (CFU-GM) and the decrease in absolute neutrophil count [Toxicol. Pathol.

21 (1993) 241]. Recently, the prevalidation of a model for predicting acute neutropenia by the CFU-GM assay has been reported [Toxicol. In Vitro 15 (2001) 729]. The model was based on prediction of human MTD by adjusting the animal-derived MTD for the differential sensitivity between CFU-GM from animal species and humans. In this study, this model has been applied on a new antitumoral drug, Yondelis (Ecteinascidin; ET-743). Preclinical studies showed that hematotoxicity was the main side effect in mice, being the MTD of 600 microg/m2 [Drugs Future 21 (1996) 1155]. The sensitivity of myeloid progenitors was higher in mice than in humans, with IC90 values of 0.69+/-0.22 nM and 1.31+/-0.21 nM for murine and human CFU-GMs respectively. This study predicts a human MTD of 1145 microg/m2. The reported human MTD of ET-743 given as a 24-h continuous infusion every 3 weeks is 1800 microg/m2 [J. Clin. Oncol. 19 (2001) 1256]. Since our predicted MTD is within fourfold of the actual MTD (the interspecies variation in tolerated dose due to differences in clearance rates, metabolism pathways and infusion rate) the result confirms the profit of the prediction model.

L5 ANSWER 14 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003464181 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12932661
TITLE: Phase I and pharmacokinetic study of Yondelis (Ecteinascidin-743; ET-743) administered as an infusion over 1 h or 3 h every 21 days in patients with solid tumours.
AUTHOR: Twelves C; Hoekman K; Bowman A; Vermorken J B; Anthoney A; Smyth J; van Kesteren C; Beijnen J H; Uiters J; Wanders J; Gomez J; Guzman C; Jimeno J; Hanauske A
CORPORATE SOURCE: Cancer Research UK, University of Glasgow, G61 1BD Glasgow, UK.. c.twelves@bradford.ac.uk
SOURCE: European journal of cancer (Oxford, England : 1990), (2003 Sep) Vol. 39, No. 13, pp. 1842-51.
Journal code: 9005373. ISSN: 0959-8049.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 8 Oct 2003
Last Updated on STN: 24 Oct 2003
Entered Medline: 23 Oct 2003

AB Yondelis (ET-743) is a novel anticancer agent isolated from the marine ascidian Ecteinascidia turbinata. ET-743 possesses potent antitumour activity and a novel mechanism of action at the level of gene transcription. We conducted two sequential phase I dose escalation and pharmacokinetic studies of ET-743 given as a 1- or a 3-h intravenous (i.v.) infusion. Seventy-two adults with metastatic or advanced solid tumours received ET-743 in escalating doses between 50 and 1100 microg/m(2), initially as a 1-h infusion, and later at doses between 1000 and 1800 microg/m(2) as a 3-h infusion every 3 weeks. The maximum tolerated dose (MTD) of ET-743 was 1100 microg/m(2) for the 1-h infusion schedule and 1800 microg/m(2) when given as a 3-h infusion. Dose-limiting toxicities (DLTs) were fatigue, neutropenia and thrombocytopenia. Transient non-cumulatives grade 3-4 increase in transaminases (not considered DLT) and grades 3-4 nausea and vomiting were frequently observed. Other toxicities (maximum grade 3) included anaemia, increased lactate dehydrogenase (LDH), bilirubin and alkaline phosphatase serum levels, and phlebitis; there were no toxic deaths. One pCR (melanoma), CR (uterine leiomyosarcoma), one PR

(colon stromal sarcoma) and a MR (37% tumour shrinkage, gastric stromal sarcoma) were observed. A further 9 patients with colorectal, mesothelioma, bile duct carcinoma and bladder cancer had SD which lasted for six or more treatment cycles. ET-743 pharmacokinetics were linear with the 3-h infusion schedule. The haematological and hepatic toxicities of ET-743 were dose-dependent and not cumulative. Based on the current trial, the recommended dose of ET-743 for phase II studies is 1650 microg/m(2) given as a 3-h infusion.

L5 ANSWER 15 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003376131 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12910529
TITLE: Phase II study of ecteinascidin 743 in heavily pretreated patients with recurrent osteosarcoma.
AUTHOR: Laverdiere Caroline; Kolb E Anders; Supko Jeffrey G; Gorlick Richard; Meyers Paul A; Maki Robert G; Wexler Leonard; Demetri George D; Healey John H; Huvos Andrew G; Goorin Allen M; Bagatell Rochelle; Ruiz-Casado Ana; Guzman Cecilia; Jimeno Jose; Harmon David
CORPORATE SOURCE: Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
CONTRACT NUMBER: P01-CA47179 (United States NCI NIH HHS)
SOURCE: Cancer, (2003 Aug 15) Vol. 98, No. 4, pp. 832-40. Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) (CLINICAL TRIAL, PHASE II) Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 13 Aug 2003 Last Updated on STN: 30 Aug 2003 Entered Medline: 29 Aug 2003
AB BACKGROUND: Recurrent osteosarcoma is a drug-resistant disease with a dismal prognosis. The objective of this Phase II study was to evaluate the activity of ecteinascidin 743 (ET-743) as a salvage therapy in these patients. METHODS: Patients with recurrent osteosarcoma who had received standard chemotherapeutic agents were eligible. ET-743 was administered at a dose of 1500 microg/m(2) as a 24-hour infusion every 3 weeks. Pharmacokinetic studies were performed during the first cycle. RESULTS: Twenty-five patients were enrolled, 23 of whom were assessable for response (median age of 18 years; range, 12-67 years). The median number of previous chemotherapeutic agents was five (range, three to eight previous agents). Sixty-one cycles were administered (median number of cycles per patient was 2; range, 1-9 cycles per patient). Three patients (12%) achieved minor responses (49% 36% and 25%, respectively). Fifteen patients (60%) developed a transient elevation of hepatic transaminases (Grade 3 or 4 [according to the National Cancer Institute Common Toxicity Criteria]), which was not cumulative. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 12 patients (48%) and 6 patients (24%), respectively. The mean area under the curve (AUC) in 4 patients experiencing Grade 4 toxicity (76.4 +/- 29.3 ng x hr/mL) was significantly greater (P = 0.034) than that in those for whom the most severe toxicity was Grade 3 (39.5 +/- 17.2 ng x hr/mL [n = 12]) or Grade 1-2 (52.6 +/- 15.6 ng x hr/mL [n = 5]). There were no other significant correlations found between pharmacokinetic variables and patient characteristics, toxicity, or therapeutic response. CONCLUSIONS: ET-743 was found to be

well tolerated in heavily pretreated osteosarcoma patients but had limited antitumor activity as a single agent. The combination of ET-743 with cisplatin or doxorubicin should be considered. Copyright 2003 American Cancer Society.DOI 10.1002/cncr.11563

L5 ANSWER 16 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003010063 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12490740
TITLE: A phase II and pharmacokinetic study of ecteinascidin 743 in patients with gastrointestinal stromal tumors.
AUTHOR: Ryan David P; Puchalski Thomas; Supko Jeffrey G; Harmon David; Maki Robert; Garcia-Carbonero Rocio; Kuhlman Caroline; Winkelman Jennifer; Merriam Priscilla; Quigley Travis; Jimeno Jose; Manola Judith; Demetri George D
CORPORATE SOURCE: Division of Hematology-Oncology, Massachusetts General Hospital, Harvard Medical School, 100 Blossom Street, Boston, MA 02114, USA.. dpryan@partners.org
SOURCE: The oncologist, (2002) Vol. 7, No. 6, pp. 531-8. Journal code: 9607837. ISSN: 1083-7159.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) (CLINICAL TRIAL, PHASE II) Journal; Article; (JOURNAL ARTICLE) (MULTICENTER STUDY) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 9 Jan 2003 Last Updated on STN: 7 Feb 2003 Entered Medline: 6 Feb 2003
AB PURPOSE: To assess the efficacy, tolerability, and pharmacokinetics of ecteinascidin 743 (ET-743) in patients with advanced gastrointestinal stromal tumors (GISTs). PATIENTS AND METHODS: The study was confined to adult patients with radiographically measurable GISTs. ET-743 was administered as a 24-hour continuous i.v. infusion at a dose of 1.5 mg/m(2) repeated every 3 weeks. Pharmacokinetic blood sampling was performed during the first cycle of therapy. Tumors were restaged after every second cycle of therapy. RESULTS: A total of 20 patients was enrolled in the study, 19 of whom were treated with 47 cycles of ET-743 (median 2, range 1-10). Severe toxicities were limited to reversible grade 3 transaminitis in 10 patients and grade 3 fatigue in one patient. There were no objective responses, and disease stabilization occurred in two patients lasting for periods of 4 and 10 months. The 1-year survival rate was 71.1%. Mean +/- standard deviation values of the maximum plasma concentration and total plasma clearance were 1.1 +/- 0.4 ng/ml and 44 +/- 16 l/h/m(2), respectively, for 19 of the 20 patients. CONCLUSION: This study is the first report of a prospective phase II trial to evaluate a cytotoxic agent in patients with GISTs. This study underscores the primary resistance of GISTS to chemotherapy and stands in stark contrast to the encouraging results recently achieved with STI571. The lack of response may be associated with a therapeutically ineffective exposure to the drug based upon the lower incidence of severe toxicities and greater clearance than described in phase I and II trials of ET-743.

L5 ANSWER 17 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2002495269 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12357306
TITLE: Pharmacokinetics of ecteinascidin 743 administered as a 24-h continuous intravenous infusion to adult patients with soft tissue sarcomas:

associations with clinical characteristics, pathophysiological variables and toxicity.

AUTHOR: Puchalski Thomas A; Ryan David P; Garcia-Carbonero Rocio; Demetri George D; Butkiewicz Leah; Harmon David; Seiden Michael V; Maki Robert G; Lopez-Lazaro Luis; Jimeno Jose; Guzman Cecilia; Supko Jeffrey G

CORPORATE SOURCE: Dana-Farber/Partners Cancer Care, Harvard Medical School, Boston, Massachusetts, USA.

SOURCE: Cancer chemotherapy and pharmacology, (2002 Oct) Vol. 50, No. 4, pp. 309-19. Electronic Publication: 2002-07-31. Journal code: 7806519. ISSN: 0344-5704.

PUB. COUNTRY: Germany: Germany, Federal Republic of

DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200211

ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 22 Nov 2002

AB PURPOSE: Ecteinascidin 743 (ET-743) is a potent cytotoxic alkaloid of marine origin that has shown promising evidence of antitumor activity during phase I clinical trials. In the study reported here, the influence of clinical characteristics and pretreatment pathophysiological variables on the pharmacokinetics of ET-743 and their associations with drug-related toxicity was examined in sarcoma patients treated in three phase II clinical trials. METHODS: Adult patients with various histological subtypes of soft tissue sarcoma received 1.5 mg/m(2) of ET-743 by 24-h continuous i.v. infusion once every 3 weeks. Eligibility criteria were similar for each study, except for the histological subtype of the tumor or the extent of prior treatment with other anticancer agents, and all patients had normal or near-normal liver and renal function. The maximum plasma concentration (C(max)) and area under the plasma profile from time zero to infinity (AUC) of the drug were determined during the first cycle of therapy. Patients were evaluated for toxicity every week. RESULTS: Geometric mean +/- SD values of the pharmacokinetic parameters in 69 patients were: C(max) 1.14 +/- 0.52 ng/ml, AUC 39.9 +/- 16.6 ng.h/ml, and total body clearance (CL) 36.7 +/- 16.4 l/h per m(2). The only significant correlation involving physical characteristics of the patients or pretreatment pathophysiological variables was a very weak relationship between alkaline phosphatase and AUC ($r=0.39$, $P<0.01$). The 15 patients with any baseline liver function test exceeding the upper limit of the normal ranges had a significantly greater ($P=0.02$) incidence of severe toxicity (80% vs 44%). Although the mean AUC of ET-743 in patients with elevated serum levels of hepatic enzymes was 17% greater than that in patients with normal pretreatment liver function tests, the difference was not significant ($P=0.22$). In addition, there was no distinct relationship between the grade of the most severe drug-related toxicity that occurred during the first cycle of therapy and the AUC for the entire cohort. The CL of ET-743 was found to be 27% greater in patients concurrently receiving dexamethasone as a preventative antiemetic than in those who were not, but the difference did not achieve statistical significance ($P=0.08$). There were no significant associations between CL (liters per hour) and body surface area or any other variable related to body size. CONCLUSIONS: The risk of developing severe toxicity was substantially enhanced in patients with relatively moderate indications of hepatic dysfunction without a coincident effect on the CL of ET-743. Dexamethasone cotreatment appeared to decrease the incidence of severe toxicity as well as the AUC of the drug. Delivering a fixed amount of drug without adjustment for the height or weight of the patient may be

more appropriate than dose normalization due to the absence of an association between CL and body surface area. Optimizing dosing strategies to further enhance the therapeutic index of ET-743 may depend upon obtaining a better understanding of the metabolic fate of the drug in humans.

L5 ANSWER 18 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2002418777 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12173492
TITLE: ET-743: the US experience in sarcomas of soft tissues.
AUTHOR: Demetri George D
CORPORATE SOURCE: Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA.. gdemetri@partners.org
SOURCE: Anti-cancer drugs, (2002 May) Vol. 13 Suppl 1, pp. S7-9. Ref: 9
Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 14 Aug 2002
Last Updated on STN: 18 Dec 2002
Entered Medline: 17 Dec 2002
AB Ecteinascidin-743 (ET-743) has shown promise as a new and effective treatment for soft-tissue sarcomas. Two independent, multicenter, Phase II studies have been performed in the USA for patients with unresectable soft-tissue sarcomas (either chemotherapy-naive or pretreated patients). The patients received ET-743 at a dose of 1500 micrograms/m2 as a 24 h continuous intravenous infusion every 3 weeks on an outpatient basis. Assessments were conducted every 6 weeks until documented progressive disease, unacceptable toxicity, or withdrawal. Responses were assessed in accordance with conventional oncological criteria and toxicities were graded using the National Cancer Institute common toxicity criteria. A total of 72 patients were enrolled: 36 patients to each study. Confirmed objective response rates were 14% (95% confidence interval (CI) 5 to 30%) and 8% (95% CI 2 to 23%) in chemotherapy-naive and pretreated patients, respectively. In chemotherapy-naive patients, 12-month progression-free and overall survival rates were 18% (95% CI 4 to 32%) and 49% (95% CI 20 to 78%), respectively. For patients with progressive disease despite prior conventional chemotherapy, 12-month progression-free and overall survival rates were 11% (95% CI 2 to 24%) and 55% (95% CI 35 to 75%), respectively. The median duration of response was 11 months. The durability of major responses in a subset of patients was impressive, as was the number of patients who achieved disease stabilization without showing objective response. Overall, ET-743 had a favorable safety profile. The most common grade 3-4 toxicities included neutropenia and transiently increased transaminase concentrations. ET-743 did not cause alopecia, mucositis, cardiotoxicity or neurotoxicity. The side effects were reversible, non-cumulative and manageable. There were no treatment-associated deaths. In conclusion, ET-743 is an active chemotherapeutic agent that can induce objective responses and clinical benefit in a subset of patients with metastatic or advanced soft-tissue sarcoma.

L5 ANSWER 19 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2002418774 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12173489

TITLE: Safety and efficacy of ET-743: the French experience.
AUTHOR: Brain Etienne G C
CORPORATE SOURCE: Department of Medical Oncology, Cancer Centre Rene Huguenin, 35 rue Dailly, 92210 Saint-Cloud, France.. e.brain@stcloud-huguenin.org
SOURCE: Anti-cancer drugs, (2002 May) Vol. 13 Suppl 1, pp. S11-4. Ref: 12
Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 14 Aug 2002
Last Updated on STN: 18 Dec 2002
Entered Medline: 17 Dec 2002

AB Initial evidence of clinical benefit with ecteinascidin-743 (ET-743) in patients with sarcoma was provided during a Phase I pharmacokinetic study in which 52 patients received ET-743 at doses of 50-1800 micrograms/m2 as a 24 h continuous infusion every 3 weeks. Neutropenia and thrombocytopenia were the dose-limiting toxicities; liver toxicity (a severe but transient and reversible increase in transaminase concentrations) was not treatment limiting. In conjunction with results obtained with ET-743 in a compassionate-use program, these indications of activity in heavily pretreated patients with sarcoma prompted initiation of a French multicenter Phase II study of ET-743 in this population. From February 1999 to January 2001, 54 patients with advanced anthracycline-pretreated soft-tissue sarcoma (STS) received ET-743 at a dose of 1500 micrograms/m2 every 3 weeks by continuous 24 h infusion. The main histological subtype was leiomyosarcoma (37%); the majority of primary tumors were visceral (24%) or uterine (19%) sarcomas. In this Phase II population (> or = 25% negative prognostic or predictive factors of response to chemotherapy; > or = 50% anthracycline- and ifosfamide-resistant), safety data were comparable to those obtained in the Phase I and compassionate-use studies. Asymptomatic and reversible neutropenia and transaminitis (grade 3/4) were the most frequent toxicities (approximately 60% of patients); febrile neutropenia was infrequent (< 10%). No mucositis, alopecia, cardiac or neurotoxicity was observed. Two severe cases of rhabdomyolysis occurred. Side effects were non-cumulative, reversible and manageable. Of 52 evaluable patients, three (6%) achieved a long-lasting (8-13 months) partial response, four (8%) achieved a minor response (25-50% tumor reduction) and 22 (42%) achieved disease stabilization. With a 13-month median follow-up, median survival was almost 11 months. Progression-free survival at 6 months was 26.5% and the overall survival rate at 12 months was almost 50%. The response rate was uninfluenced by tumor metastatic site, size or anthracycline sensitivity status. These results, combined with the lack of cumulative toxicity, confirm the role of ET-743 in the treatment of advanced STS.

L5 ANSWER 20 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2002098440 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11801542
TITLE: A phase I and pharmacokinetic study of ecteinascidin-743 on a daily x 5 schedule in patients with solid malignancies.
AUTHOR: Villalona-Calero Miguel A; Eckhardt S Gail; Weiss Geoffrey; Hidalgo Manuel; Beijnen Jos H; van Kesteren Charlotte; Rosing Hilde; Campbell Elizabeth; Kraynak Maura; Lopez-Lazaro Luis; Guzman Cecilia; Von Hoff Daniel D;

Jimeno Jose; Rowinsky Eric K
CORPORATE SOURCE: Institute for Drug Development, Cancer Therapy and Research Center, The University of Texas Health Science Center at San Antonio, 78229, USA.. villalona-1@medctr.osu.edu
CONTRACT NUMBER: M01 RR01346 (United States NCRR NIH HHS)
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2002 Jan) Vol. 8, No. 1, pp. 75-85.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 7 Feb 2002
Last Updated on STN: 12 Apr 2002
Entered Medline: 11 Apr 2002

AB PURPOSE: The purpose of this study was to (a) assess the feasibility of administering ecteinascidin-743 (ET-743), a novel DNA minor-groove disrupting agent of marine origin, administered as a daily i.v. infusion for 5 days every 3 weeks; (b) recommend a dose for Phase II studies; (c) characterize its pharmacokinetic behavior; and (d) seek preliminary evidence of anticancer activity. EXPERIMENTAL DESIGN: Patients with advanced solid malignancies were treated with escalating doses of ET-743 as a daily 1-h i.v. infusion for 5 days every 3 weeks. Plasma and urine were sampled on both days 1 and 5 of the first course. Pharmacokinetic parameters were related to the principal toxicities. RESULTS: Forty-two patients were treated with 118 courses of ET-743 at doses ranging from 6 to 380 microg/m(2)/day. Elevations in hepatic transaminases were common at ET-743 dose levels > or =216 microg/m(2)/day, resolved rapidly, and were never dose limiting nor cumulative. Instead, hematological toxicity was the principal toxicity that precluded dose escalation. The maximum tolerated dose of ET-743 that could be administered repetitively was 325 microg/m(2)/day. Antitumor activity was noted in three patients with leiomyosarcoma and primary peritoneal and ovarian carcinomas. The pharmacokinetics of ET-743 were dose independent, and drug accumulation over the 5 days of treatment was modest, with the ratio of the area under the plasma-versus-time curve on day 5 to that on day 1 averaging 2.05. The volume of distribution at steady state was large (mean, 1037 liters/m(2)), and the mean terminal half life on day 5 was 26.81 h. CONCLUSIONS: The maximum tolerated dose of ET-743 that can be administered repetitively is 325 microg/m(2)/day daily x 5 every 3 weeks, which is recommended for disease-directed clinical trials. The acceptable toxicity profile of ET-743 on the divided-dose schedule evaluated in this trial, as well as the generally superior antitumor activity associated with divided-dose schedules in preclinical studies, provides a rationale for further evaluation of ET-743 on this administration schedule.

L5 ANSWER 21 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2001184563 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11230466
TITLE: Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors.
AUTHOR: Taamma A; Misset J L; Riofrio M; Guzman C; Brain E; Lopez Lazaro L; Rosing H; Jimeno J M; Cvitkovic E

CORPORATE SOURCE: Hopital Paul Brousse, Villejuif, France.
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2001 Mar 1) Vol. 19, No. 5, pp. 1256-65.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 4 Apr 2001
Last Updated on STN: 4 Apr 2001
Entered Medline: 29 Mar 2001

AB PURPOSE: To define the maximum-tolerated dose (MTD) and the phase II recommended dose (RD) of ecteinascidin-743 (ET-743) given as a 24-hour continuous infusion every 3 weeks to patients with treatment-refractory solid tumors. PATIENTS AND METHODS: Fifty-two patients received a total of 158 cycles of ET-743 at one of nine dose levels (DLs) ranging from 50 to 1,800 microg/m(2). RESULTS: The MTD was defined as 1,800 microg/m(2) (DL 9), and the phase II RD was 1,500 microg/m(2) (DL 8) for moderately pretreated patients with performance status (PS) 0 to 1 and good hepatobiliary function. Neutropenia and thrombocytopenia were the dose-limiting toxicities (DLTs) and were severe at the MTD (1,800 microg/m(2)) in 94% and 25% of cycles, respectively. At the RD (1,500 microg/m(2)), neutropenia and thrombocytopenia were present in 33% and 10% of cycles, respectively. Transient acute elevated transaminase levels occurred in almost all cycles and was severe in 38% of cycles. Severe toxicities and DLTs were observed in patients with poor PS or abnormal liver function or who had received a large number of previous chemotherapy regimens. Antitumor activity was observed at the three highest DLs, including three partial responses (breast cancer, osteosarcoma, and liposarcoma), and four patients (all with progressing soft tissue sarcomas) had stable disease lasting > or = 3 months. Pharmacokinetic studies were performed on all patients for at least the first cycle, giving a linear pharmacokinetic profile; this showed a relationship between area under the curve (AUC) and transaminitis grade and a clear correlation between AUC and severe hematologic toxicity likelihood. CONCLUSION: The RD for a 24-hour continuous intravenous infusion of ET-743 is 1,500 microg/m(2), with the most prevalent DLTs being hematologic. Patients with minor baseline hepatobiliary function abnormalities have a higher likelihood of severe hematologic toxicities and AUC-related DLTs, requiring dose adjustments or delays.

L5 ANSWER 22 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2001184562 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11230465
TITLE: Ecteinascidin-743: a marine-derived compound in advanced, pretreated sarcoma patients--preliminary evidence of activity.
AUTHOR: Delaloge S; Yovine A; Taamma A; Riofrio M; Brain E; Raymond E; Cottu P; Goldwasser F; Jimeno J; Misset J L; Marty M; Cvitkovic E
CORPORATE SOURCE: Hopital Paul Brousse and Institut Gustave Roussy, Villejuif, France.
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2001 Mar 1) Vol. 19, No. 5, pp. 1248-55.
Journal code: 8309333. ISSN: 0732-183X.

PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 4 Apr 2001
Last Updated on STN: 4 Apr 2001
Entered Medline: 29 Mar 2001

AB PURPOSE: To report the activity of the chemotherapeutic agent ecteinascidin-743 (ET-743) in advanced pretreated sarcoma patients observed during a phase I study and a named-patient basis, compassionate use program. PATIENTS AND METHODS: Twenty-nine pretreated, advanced soft tissue sarcoma (STS) and bone sarcoma patients consecutively seen in our centers were included, 12 from a phase I trial and 17 from a compassionate use program cohort. Patients were treated every 3 weeks at either 1,200 microg/m(2) (six patients), 1,500 microg/m(2) (the recommended dose, 22 patients), or 1,800 microg/m(2) (the maximum-tolerated dose, one patient), given as a 24-hour infusion every 3 to 4 weeks. RESULTS: Fifteen men and 14 women were treated. The median patient age was 46 years (range, 16 to 71 years), with a median World Health Organization performance status of 1 (range, 0 to 2). Twenty-five patients had STS, three had osteosarcoma, and one had Ewing's sarcoma, and all had progressive disease at accrual. Fifteen patients had bulky disease, and 14 had clinical resistance to anthracyclines. A total of 136 treatment cycles were administered (median per patient, five cycles; range, one to 12 cycles). Transient grade 3 and 4 transaminitis was reported in 24% and 5% of cycles, respectively, grade 3 to 4 neutropenia occurred in 32% of cycles, with concomitant sporadic grade 3 to 4 thrombocytopenia in 5.1% of cycles. Grade 2 to 3 asthenia occurred in 21% of cycles. There were two partial responses (PRs) in STS patients and two PRs in osteosarcoma patients. Two minor responses and 10 disease stabilizations were seen. Median duration of response was 10.5 months (range, 2.8 to 15 months), and mean duration of stabilization was 5.2 months. CONCLUSION: ET-743 has activity in advanced, highly pretreated STS and osteosarcoma patients and warrants further trials to establish the extent of its activity in this setting.

L5 ANSWER 23 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2008:334549 USPATFULL
TITLE: Prognostic Molecular Markers
INVENTOR(S): Rosell Costa, Rafael, Barcelona, SPAIN
Taron Roca, Miguel, Barcelona, SPAIN
Jimeno Donaque, Jose Maria, Madrid, SPAIN
Tercero Lopez, Juan Carlos, Madrid, SPAIN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20080293725	A1	20081127	
APPLICATION INFO.:	US 2005-571589	A1	20050711	(11)
	WO 2005-EP7605		20050711	
			20070205	PCT 371 date

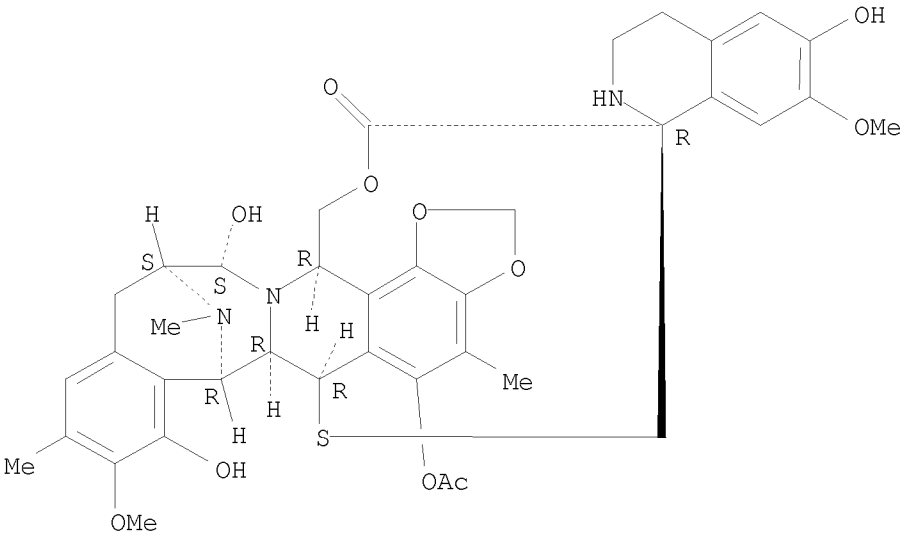
	NUMBER	DATE
PRIORITY INFORMATION:	EP 2004-76997	20040709

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: KING & SPALDING, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036-4003, US
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 825
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the use of ecteinascidin 743 in patients having certain levels of molecular markers who can predict the outcome of chemotherapy, in particular in patients having low levels of BRCA1 expression.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, ET-743
(BRCA1 as marker in treatment of cancer patients with ecteinascidin 743)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 24 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2008:291098 USPATFULL
TITLE: Combination Therapy Comprising the Use of Et-743 and Paclitaxel for Treating Cancer
INVENTOR(S): Rowinsky, Eric, San Antonio, TX, UNITED STATES
Chu, Quincy Siu-Ching, San Antonio, TX, UNITED STATES
Donaque, Jose Maria Jimeno, Madrid, SPAIN
Lazaro, Luis Lopez, Madrid, SPAIN

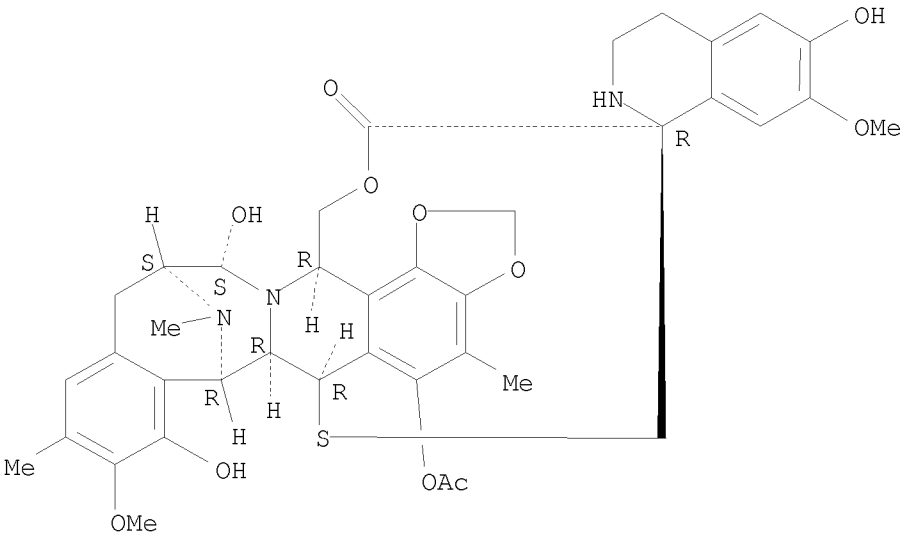
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20080255132	A1	20081016	
APPLICATION INFO.:	US 2004-579130	A1	20041028	(10)
	WO 2004-US35779		20041028	
			20070813	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-520330P	20031114 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KING & SPALDING, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036-4003, US
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 419
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treating a human body for cancer are provided. In one aspect, an effective therapeutic amount of paclitaxel is administered in combination with ET-743 in a dose range between 0.5 and 1 mg/m.sup.2. In a related aspect, an effective therapeutic amount of ET-743 is administered in combination with paclitaxel in a dose range between 80 and 140 mg/m.sup.2.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, ET-743
(ET-743 combination with paclitaxel for treatment of cancer)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 25 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2008:129925 USPATFULL
TITLE: IGFBP2 BIOMARKER
INVENTOR(S): Wang, Yan, Scotch Plains, NJ, UNITED STATES
PATENT ASSIGNEE(S): Schering Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080112888	A1	20080515

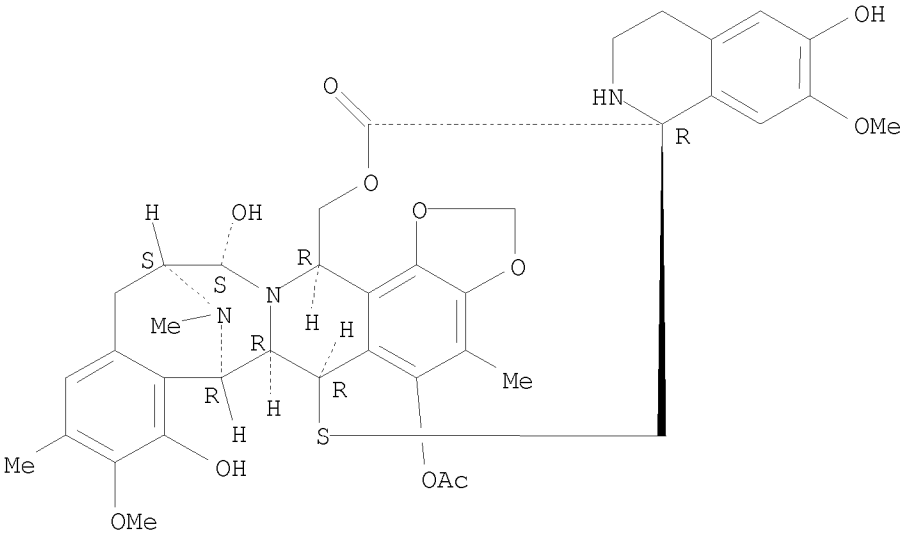
APPLICATION INFO.: US 2007-771454 A1 20070629 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-818004P	20060630 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530, US
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
LINE COUNT: 6004
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides method for quickly and conveniently determining if a given treatment regimen of IGF1R inhibitor is sufficient, e.g., to saturate IGF1R receptors in the body of a subject. Several clinically relevant determinations may be made based on this point, including, for example, whether the dosage of the regimen is sufficient or should be increased.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, Trabectedin
(cancer therapy using; blood levels of IGBP2 as marker for monitoring effectiveness of inhibitors of IGF1 receptors in cancer therapy)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 26 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2007:315737 USPATFULL
TITLE: Compositions and Uses of Et 743 for Treating Cancer
INVENTOR(S): Cvitkovich, Esteban, Paris, FRANCE
Demetri, George Daniel, Boston, MA, UNITED STATES

Guzman, Cecilia, Madrid, SPAIN
Jimeno, Jose, Madrid, SPAIN
Lazaro, Luis Lopez, Madrid, SPAIN
Misset, Jean Louis, Villejuif Cedex, FRANCE
Twelves, Chris, Glasgow, UNITED KINGDOM
Von Hoff, Daniel D., Tuscon, AZ, UNITED STATES
PATENT ASSIGNEE(S): Pharma Mar S.A., Madrid, SPAIN (non-U.S. corporation)

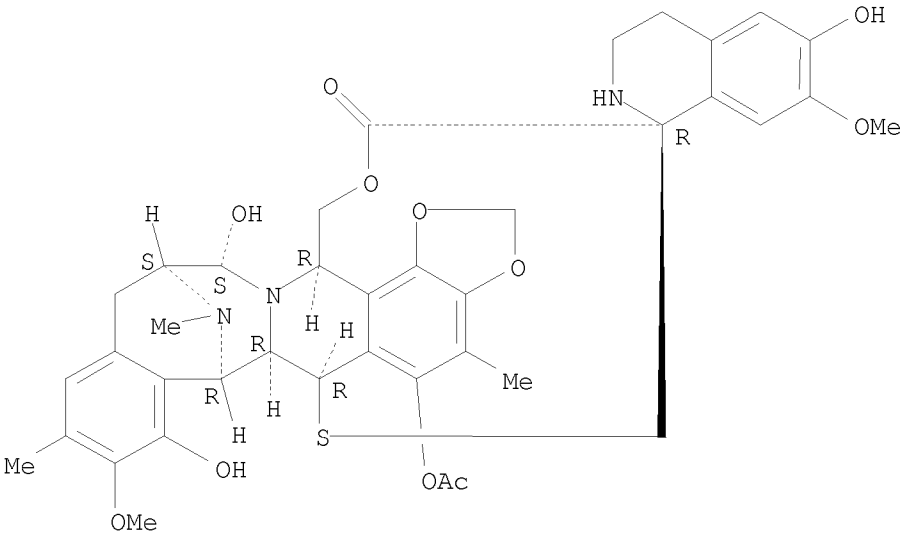
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070275942	A1	20071129
APPLICATION INFO.:	US 2007-769873	A1	20070628 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1999-11183	19990513
	GB 1999-11346	19990514
	GB 1999-27005	19991115
	GB 1999-18534	19990805
	GB 1999-27106	19991116
	GB 2000-7637	20000329

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KING & SPALDING, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036-4003, US
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 466
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Et 743 is used in the preparation of a medicament for the treatment of the human body for cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, Et 743
(Et 743; i.v. infusions of ET743 for cancer treatment)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 27 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2007:217209 USPATFULL		
TITLE:	Combination		
INVENTOR(S):	Rybak, Mary Ellen, Thousand Oak, CA, UNITED STATES		
PATENT ASSIGNEE(S):	PHARMA MAR, S.A.U., MADRID, SPAIN, E-28770 (non-U.S. corporation)		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070190164	A1	20070816	
APPLICATION INFO.:	US 2004-579160	A1	20041115	(10)
	WO 2004-GB50026		20041115	
			20070301	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-519690P	20031113 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	KING & SPALDING, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036-4003, US
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
LINE COUNT:	393

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of treating a human body for cancer are provided. In one aspect, a therapeutic amount of capecitabine is administered in combination with ET-743 in a dose range between 0.75 and 1.4 mg/M.sup.2 for Et-743. In a related aspect, an effective therapeutic amount of ET-743 is administered in combination with capecitabine in a dose range between 1500 to 2500 mg/m/day for capecitabine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

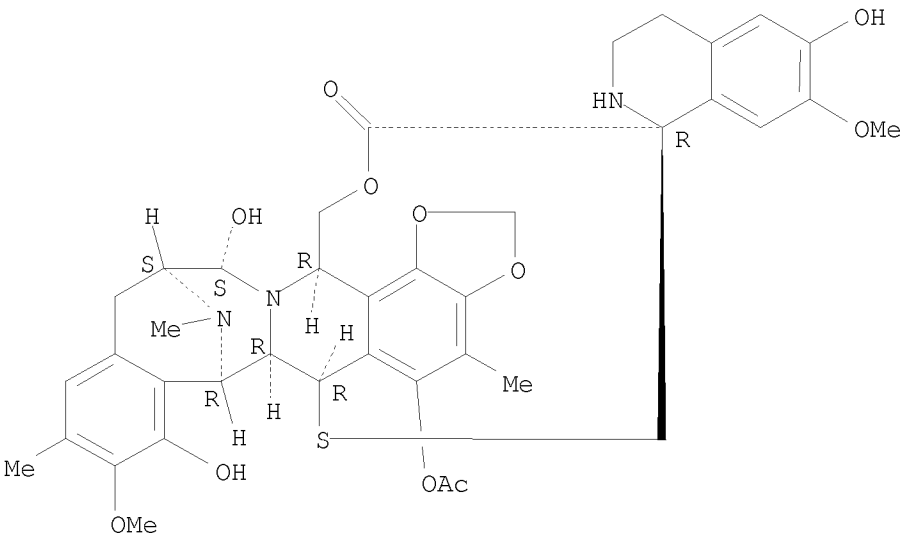
IT 114899-77-3, ET-743
(ET-743 combinations for cancer treatment)

RN 114899-77-3 USPATFULL

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-

7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 28 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2007:107685 USPATFULL
TITLE:	Synthesis of naturally occcuring ecteinascidins and related compounds
INVENTOR(S):	Martinez, Valentin, Madrid, SPAIN
PATENT ASSIGNEE(S):	Pharma Mar, S.A., Madridd, SPAIN, E-28770 (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070093658	A1	20070426	
APPLICATION INFO.:	US 2003-503106	A1	20030204	(10)
	WO 2003-GB481		20030204	
			20050608	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2002-2544	20020204

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Fish & Richardosn, 225 Franklin St., Boston, MA, 02110, US
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
LINE COUNT:	3896

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Ecteinascidin compounds with a quinone ring for ring E are active as anti-cancer agents. Related processes and compounds are provided.

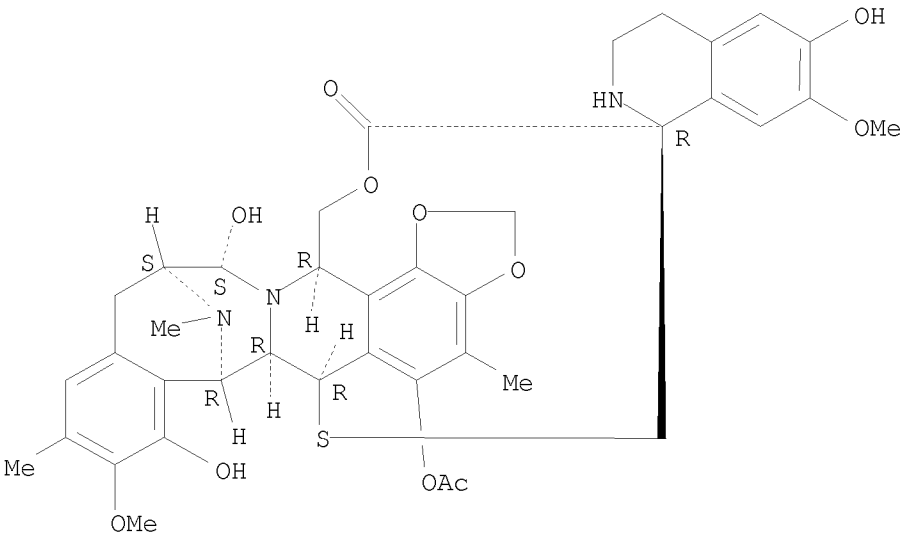
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 114899-77-3P, Et 743
(preparation of ecteinascidin derivs. for therapeutic use as antitumor agents)

RN 114899-77-3 USPATFULL

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 29 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2007:95154 USPATFULL
TITLE:	Combination therapy comprising the use of et-743 and doxorubicin for treating cancer
INVENTOR(S):	Gianni, Luca, Milan, ITALY D'Incalci, Maurizio, Milan, ITALY de Braud, Filippo, Milan, ITALY Marsoni, Silvia, Milan, ITALY Donaque, Jose Maria Jimeno, Madrid, SPAIN Lazaro, Luis Lopez, Madrid, SPAIN
PATENT ASSIGNEE(S):	Pharma Mar, S.A.U., Madrid, SPAIN, E-28770 (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070082856	A1	20070412	
APPLICATION INFO.:	US 2004-579251	A1	20041112	(10)
	WO 2004-GB50025		20041112	
			20061020	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2003-26486	20031114

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	KING & SPALDING, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036-4003, US
NUMBER OF CLAIMS:	18
EXEMPLARY CLAIM:	1
LINE COUNT:	453

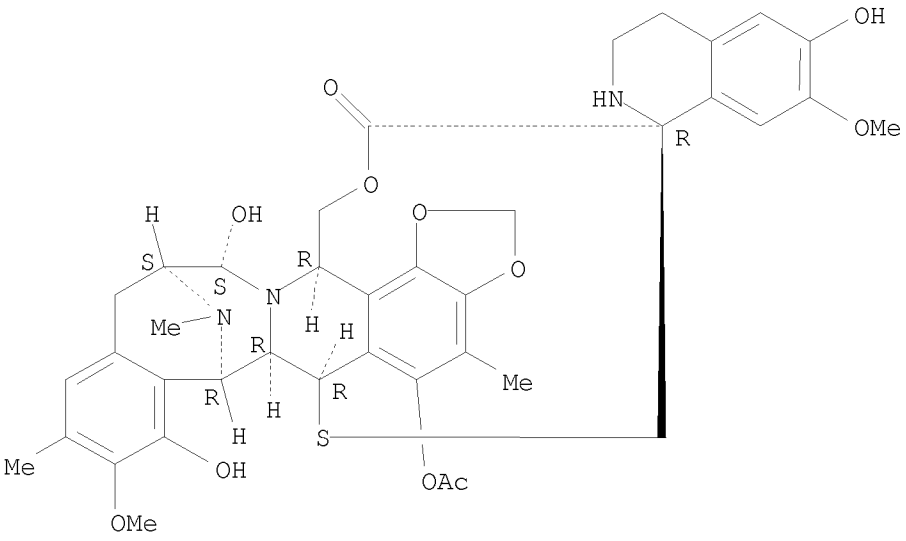
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of treating a human body for cancer are provided. In

one aspect, a therapeutic amount of doxorubicin is administered in combination with ET-743 in a dose range between 0.5 and 1 mg/m.sup.2. In a related aspect, an effective therapeutic amount of ET-743 is administered in combination with doxorubicin in a dose range between 40 and 80 mg/m.sup.2.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, ET-743
(ET-743 combination with doxorubicin for treatment of cancer)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



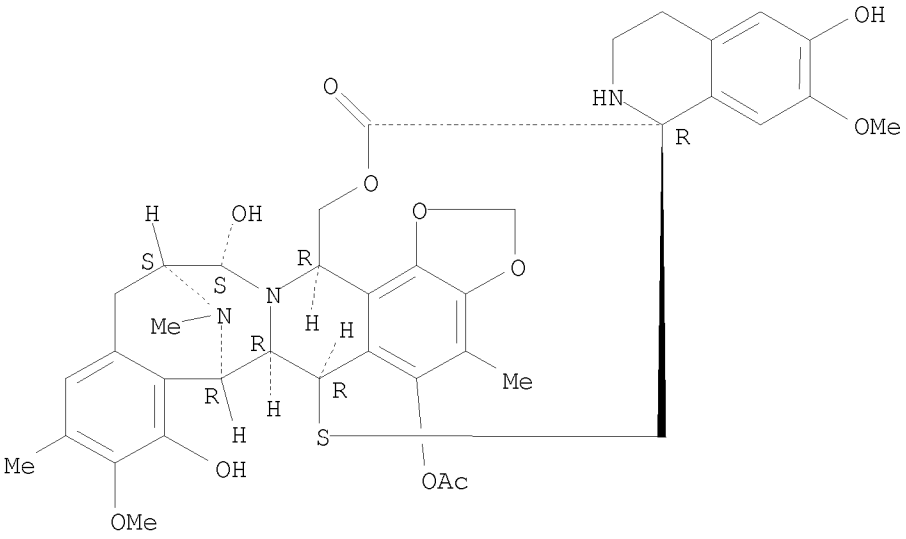
L5 ANSWER 30 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2007:5492 USPATFULL			
TITLE:	Antitumoral combinations containing et-743 and a cruciferous and a cruciferous indole compound			
INVENTOR(S):	Donald, Sarah, Leicestershire, UNITED KINGDOM Gescher, Andreas, Leicestershire, UNITED KINGDOM Donaque, Jose Maria Jimeno, Madrid, SPAIN			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070004691	A1	20070104	
APPLICATION INFO.:	US 2004-575132	A1	20041014	(10)
	WO 2004-GB4358		20041014	
			20060707	PCT 371 date
	NUMBER		DATE	
PRIORITY INFORMATION:	GB 2003-24201		20031015	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	MORGAN & FINNEGAN, L.L.P., 3 WORLD FINANCIAL CENTER, NEW YORK, NY, 10281-2101, US			

NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Administration of a cruciferous indole compound can reduce undesirable toxic side effects inherent in the anti-tumor therapy with ET-743 before during or after administration of the ET-743.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, Et743
(antitumoral combinations containing ET-743 and a cruciferous and a cruciferous indole compound)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 31 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2006:125286 USPATFULL
TITLE: New antitumoral derivatives of et-743
INVENTOR(S): Martinez, Valentin, Acala de Henares, SPAIN
Flores, Maria, Sevilla, SPAIN
Gallego, Pilar, Madrid, SPAIN
Cuevas, Carmen, Madrid, SPAIN
Munt, Simon, Madrid, SPAIN
Manzanares, Ignacio, Madrid, SPAIN

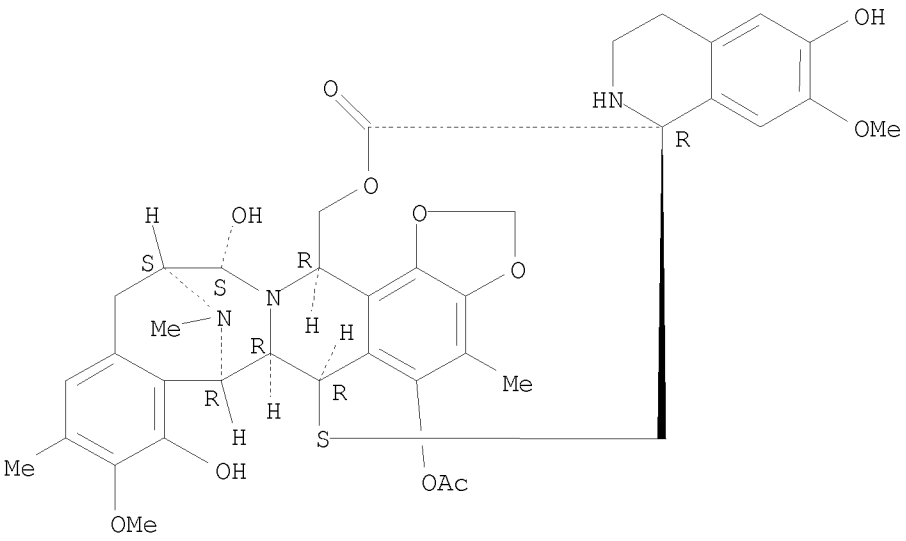
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20060106021	A1	20060518	
APPLICATION INFO.:	US 2002-484060	A1	20020717	(10)
	WO 2002-GB3288		20020717	
			20050302	PCT 371 date

	NUMBER	DATE

PRIORITY INFORMATION: GB 2001-17402 20010717
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, P.O. BOX 1022, MINNEAPOLIS, MN, 55440-1022, US
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
LINE COUNT: 5414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Derivatives of Et-743 or Et-770 or Et-729 are provided. The derivatives are of the general formula (Ia) wherein the substituent groups take various permitted meanings.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, Et 743
(preparation of ecteinascidin 743 derivs. for therapeutic use as antitumor agents)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 32 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2006:111740 USPATFULL
TITLE: Formulations
INVENTOR(S): Beijnen, Jacob Hendrik, Amsterdam, NETHERLANDS
Nuijen, Bastiaan, Amsterdam, NETHERLANDS
Salve, Pilar Calvo, Madrid, SPAIN
Barreira, Maria Tobio, Madrid, SPAIN

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20060094687	A1	20060504
APPLICATION INFO.:	US 2005-261876	A1	20051028 (11)

NUMBER DATE

PRIORITY INFORMATION:	US 2004-623813P 20041029 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MORGAN & FINNEGAN, L.L.P., 3 World Financial Center, New York, NY, 10281-2101, US
NUMBER OF CLAIMS:	35
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Page(s)
LINE COUNT:	1425

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Ecteinascidin formulations, methods of preparing the same, articles of manufacture and kits with such formulations, and methods of treating proliferative diseases with the same formulations are provided.

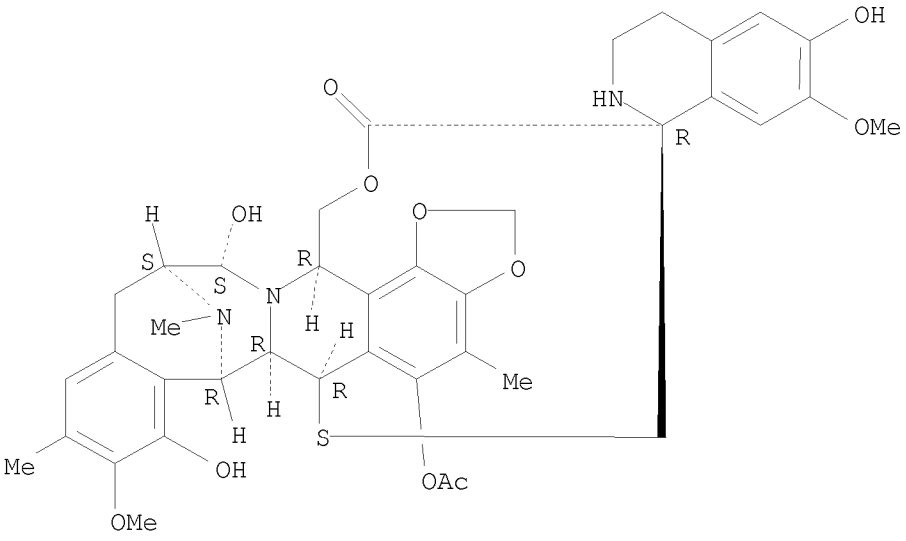
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 114899-77-3, ET-743
(ecteinascidin formulations, methods for preparation and therapeutic uses thereof)

RN 114899-77-3 USPATFULL

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 33 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2005:215496 USPATFULL
TITLE:	Combination of a Cox-2 inhibitor and a DNA topoisomerase I inhibitor for treatment of neoplasia
INVENTOR(S):	Masferrer, Jaime L., Ballwin, MO, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20050187172	A1	20050825	
APPLICATION INFO.:	US 2004-22174	A1	20041223	(11)

NUMBER DATE

PRIORITY INFORMATION:	US 2003-532203P 20031223 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49, NEW YORK, NY, 10017-5612, US
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
LINE COUNT:	4978

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides combinations of a Cox-2 inhibitor and a DNA topoisomerase inhibitor and methods of use thereof for preventing and/or treating neoplasia or or a neoplasia-related disorder in a subject.

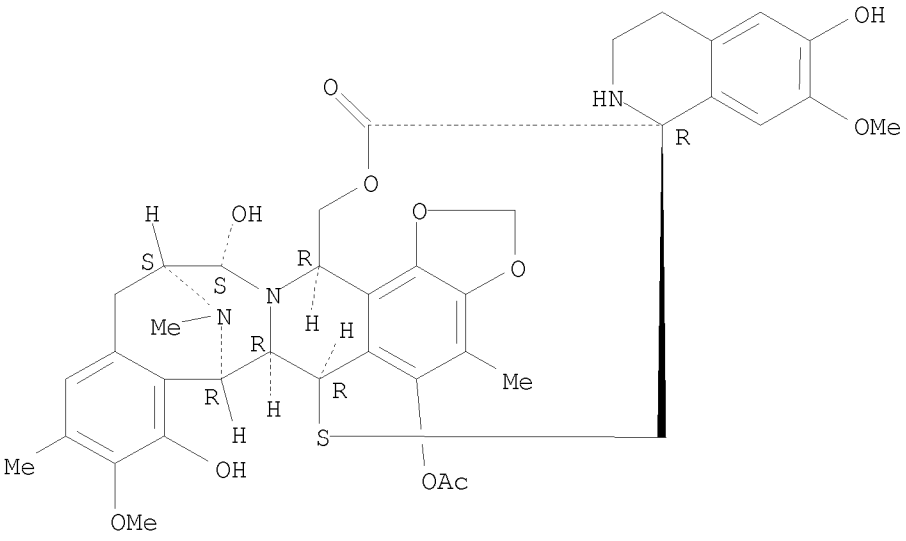
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 114899-77-3, Ecteinascidin 743
(cyclooxygenase 2 inhibitor combination with DNA topoisomerase 1 inhibitor for treatment of neoplasia)

RN 114899-77-3 USPATFULL

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 34 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2005:4912 USPATFULL
TITLE:	Use of antitumoral compound in cancer therapy
INVENTOR(S):	Jimeno, Jose, Madrid, SPAIN Casado, Ana Ruiz, Madrid, SPAIN Lazaro, Luis Lopez, Madrid, SPAIN Rowensky, Eric, San Antonio, TX, UNITED STATES Hidalgo, Manuel, Baltimore, MD, UNITED STATES

NUMBER	KIND	DATE

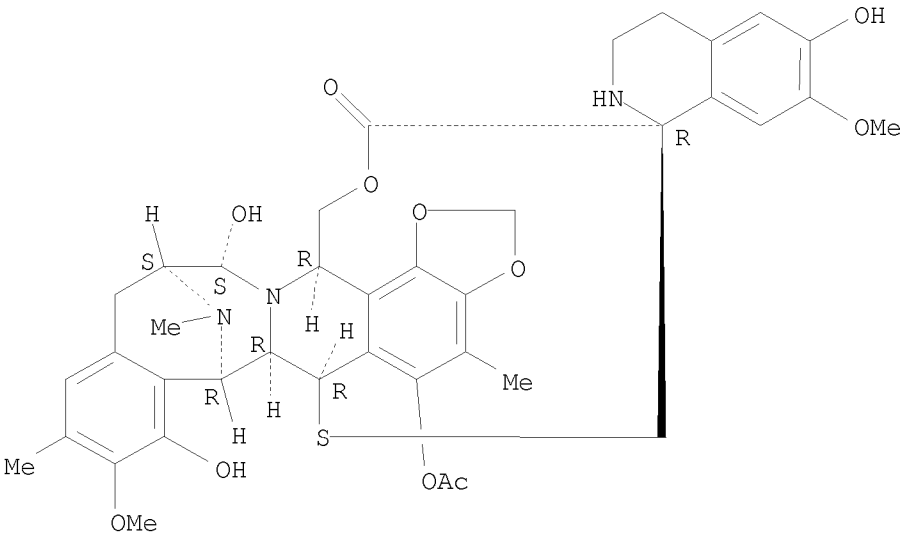
PATENT INFORMATION: US 20050004018 A1 20050106
APPLICATION INFO.: US 2004-492320 A1 20040818 (10)
WO 2002-US33548 20021021

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-348414P	20011019 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 675
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Improved dosing schedules for ecteinascidin 743 are given for treatment of cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, Ecteinascidin 743
(improved use of antitumoral compound in cancer therapy)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



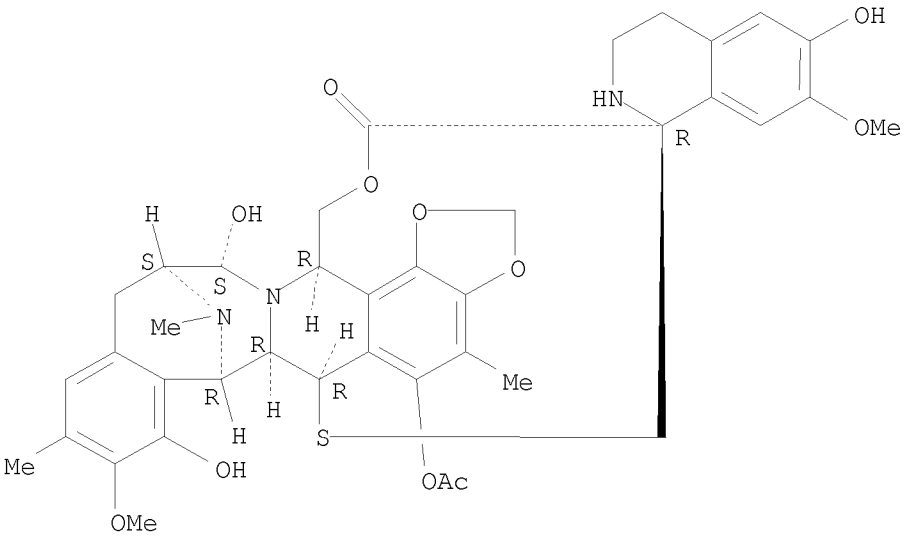
L5 ANSWER 35 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2004:142434 USPATFULL
TITLE: Effective antitumor treatments
INVENTOR(S): Takahashi, Naoto, Tokyo, JAPAN
Weitman, Steve, San Antonio, TX, UNITED STATES
D'Incalci, Maurizio, Milan, ITALY
Faircloth, Glynn Thomas, Cambridge, MA, UNITED STATES
Giavazzi, Rafaella, Bergamo, ITALY
Gescher, Andreas, Woodhouse Eves, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040108086	A1	20040610
APPLICATION INFO.:	US 2003-416086	A1	20030917 (10)
	WO 2001-GB4902		20011106

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BANNER & WITCOFF, LTD., 28 STATE STREET, 28th FLOOR, BOSTON, MA, 02109-9601
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 752
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB ET-743 is used in the preparation of a medicament for an effective treatment of a tumour by combination therapy employing ET-743 with another drug.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, ET-743
(effective antitumor treatments with combinations of ET-743 with other antitumor agents resulting in additive and synergistic interactions)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 36 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2004:70958 USPATFULL
TITLE: Cyclic protein tyrosine kinase inhibitors
INVENTOR(S): Das, Jagabandhu, Mercerville, NJ, UNITED STATES
Padmanabha, Ramesh, Hamden, CT, UNITED STATES
Chen, Ping, Belle Mead, NJ, UNITED STATES
Norris, Derek J., Trenton, NJ, UNITED STATES
Doweyko, Arthur M.P., Long Valley, NJ, UNITED STATES
Barrish, Joel C., Richboro, PA, UNITED STATES
Wityak, John, Robbinsville, NJ, UNITED STATES

Lombardo, Louis J., Belle Mead, NJ, UNITED STATES
Lee, Francis Y.F., Yardley, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040054186	A1	20040318
	US 7125875	B2	20061024
APPLICATION INFO.:	US 2003-395503	A1	20030324 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-548929, filed on 13 Apr 2000, GRANTED, Pat. No. US 6596746

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-129510P	19990415 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Stephen B. Davis, Bristol-Myers Squibb Company, Patent Department, P.O. Box 4000, Princeton, NJ, 08543-4000
NUMBER OF CLAIMS: 100
EXEMPLARY CLAIM: 1
LINE COUNT: 6602
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel cyclic compounds and salts thereof, pharmaceutical compositions containing such compounds, and methods of using such compounds in the treatment of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders.

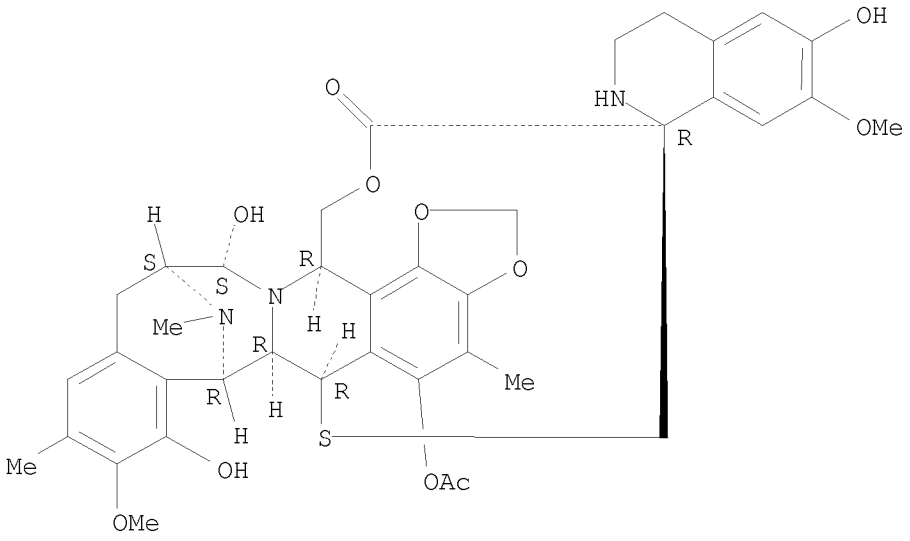
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 114899-77-3, Ecteinascidin 743
(co-administration; preparation of 5-thiazolecarboxamides as protein tyrosine kinase inhibitors for treating immunol. and oncol. disorders in combination with other agents)

RN 114899-77-3 USPATFULL

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 37 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2003:271481 USPATFULL		
TITLE:	C3-CYANO EPOTHILONE DERIVATIVES		
INVENTOR(S):	Regueiro-Ren, Alicia, Middletown, CT, UNITED STATES Kim, Soong-Hoon, Titusville, NJ, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030191089	A1	20031009
	US 6719540	B2	20040413
APPLICATION INFO.:	US 2003-386072	A1	20030311 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2002-363441P		20020312 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000		
NUMBER OF CLAIMS:	35		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1397		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compounds useful in the treatment of cancer or other proliferative diseases represented by formula I: ##STR1##

wherein:

Q is selected from the group consisting of ##STR2##

M is O, NR.sub.9, or CR.sub.10R.sub.11; X is O or NH; and the R groups are as defined, and therapeutic compositions containing them alone or in combination with other therapeutic agents useful in the treatment of cancer or other proliferative diseases.

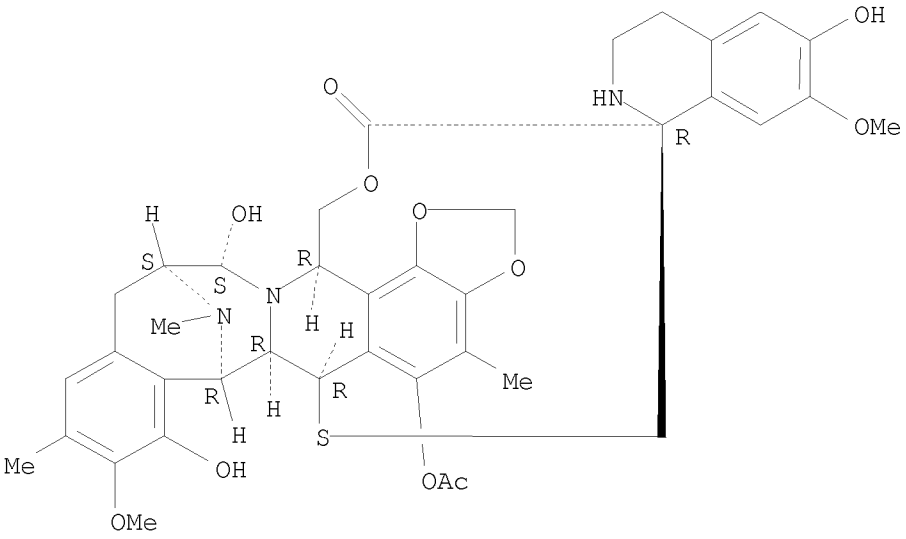
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 114899-77-3, Ecteinascidin 743
(pharmaceutical composition containing epothilone derivs and; preparation of epothilone derivs. for therapeutic use as anticancer agents)

RN 114899-77-3 USPATFULL

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L5 ANSWER 38 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2003:265948 USPATFULL
TITLE: C12-cyano epothilone derivatives
INVENTOR(S): Vite, Gregory D., Titusville, NJ, UNITED STATES
Regueiro-Ren, Alicia, Middletown, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030186965	A1	20031002
	US 7211593	B2	20070501
APPLICATION INFO.:	US 2003-386059	A1	20030311 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-363703P	20020312 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 1430
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compounds useful in the treatment of cancer or other proliferative diseases represented by the formula ##STR1##

wherein:

R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.5 are hydrogen or lower alkyl;

R.sub.6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, or heterocyclo;

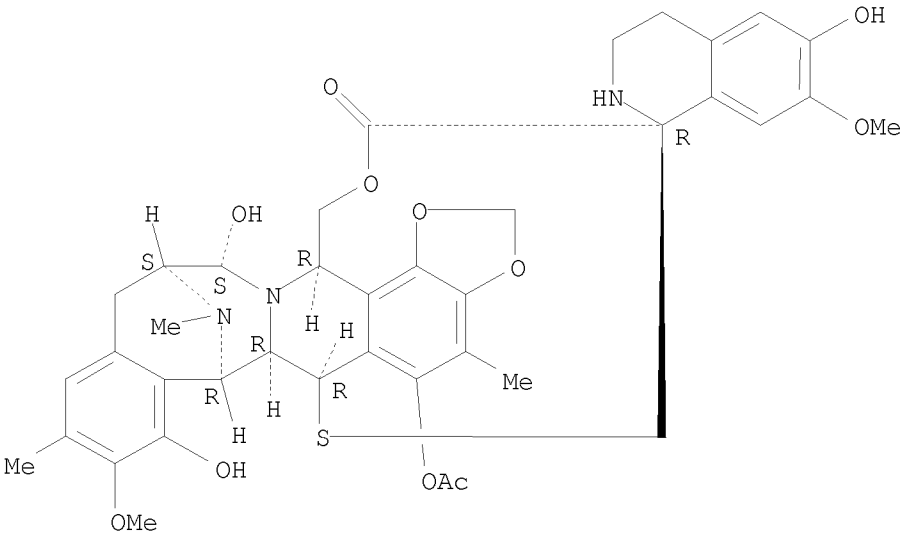
X is hydrogen and Y is hydroxy, or X and Y taken together represent a carbon-carbon bond;

and pharmaceutically acceptable salts, solvates, or hydrates thereof.

Also included are therapeutic compositions containing the compounds represented by formula I as active ingredients, alone or in combination with other therapeutic agents useful in the treatment of cancer or other proliferative diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 114899-77-3, Ecteinascidin 743
(therapeutic agent for use with C12-cyano epothilone derivs.)
RN 114899-77-3 USPATFULL
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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FILE 'REGISTRY' ENTERED AT 14:01:47 ON 08 JAN 2009
E "ET-743"/CN 25
E "ET 743"/CN 25
L1 1 S E3

FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 14:02:33 ON 08 JAN 2009
L2 559 S L1
L3 496 S L2 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM? OR ?CAR
L4 113 S L3 AND (INTRAVENOUS OR INFUSION)
L5 38 S L4 AND ("3 WEEKS" OR "4 WEEKS")

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---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	164.88	172.98

STN INTERNATIONAL LOGOFF AT 14:11:17 ON 08 JAN 2009